MEDICAL PROCEEDINGS

MEDIESE BYDRAES

A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

Registered at the General Post Office as a Newspaper

By die Hoofposkantoor as Nuusblad Geregistreer

Vol. 5 · No. 4 · 5s.

Johannesburg
21 February 1959 Februarie 21

Jaarliks £1 : 1 : 0 Yearly

IN THIS ISSUE · IN HIERDIE UITGAWE

Publishers: Juta and Co. Ltd. P.O. Box 1010 · Johannesburg: P.O. Box 30 · Cape Town

Uitgewers: Juta en Kie. Bpk. Posbus 1010 · Johannesburg: Posbus 30 · Kaapstad

Medical Proceedings · Mediese Bydraes

Vol. 5 · No. 4 INDEX · INHOUD 21 February 1959 Februarie 21

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EDITORIAL · REDAKSIONEEL

ADVERSE REACTIONS TO PENICILLIN

Warnings against indiscriminate use of penicillin have been issued by WHO experts following a comprehensive study of reports on adverse reactions to the drug.[1] The number of these reports has been steadily increasing in step with the fabulous expansion in penicillin production: from a modest 29 pounds in 1943, when the drug first came into use, world production has now grown to 750 tons annually.

This growth, unprecedented in the history of pharmacology, is further illustrated by the fact that to-day penicillin, together with hundreds of other, less common, antibiotics so far developed, represents half the value of the world's total pharmaceutical production.

In relation to this, the number of toxic and allergic reactions has so far been exceedingly small. It is, nevertheless, estimated that by 1957 about 1,000 fatal reactions to penicillin treatment had occurred in the United States of America alone, and studies in Denmark have shown that 3 fatal reactions per 10 million injections can be expected.

Reactions may become more frequent in the future as an increasing number of people are using more and more penicillin, and gradually are being sensitized to this antibiotic. At the present time, however, the risk involved in using penicillin is not greater

1. Review by O. Idsöe, R. R. Willcox (WHO consultants) and T. Guthe (Chief, Venereal Diseases and Treponematoses Section, WHO, Geneva). Published in the WHO *Bulletin*, Vol. 19, No. 3, 1958.

ONGUNSTIGE REAKSIES OP PENISILLIEN

Waarskuwings teen die onoordeelkundige gebruik van penisillien is uitgereik deur deskundiges van die Wêreldgesondheidsorganisasie wat omvattende ondersoek na verslae oor ongunstige reaksies op die middel[1] ingestel het. Die fabelagtige wyse waarop penisillienproduksie gestyg het, het 'n geleidelike toename in die aantal verslae van hierdie aard tot gevolg gehad. In 1943, toe die middel vir die eerste keer gebruik is, is 'n karige 29 pond geproduseer. Vandag het wêreldproduksie tot 750 ton per jaar gestyg.

Hierdie toename wat ongeëwenaard in die geskiedenis van die farmakologie is, word verder toegelig deur die feit dat penisillien, tesame met die honderde ander minderbekende antibiotica wat tot dusver ontwikkel is, vandag die helfte van die wêreld se totale artsenymiddelproduksie verteenwoordig.

As hierdie dinge in gedagte gehou word, is die aantal toksiese en allergiese reaksies wat tot dusver teëgekom is, buitengewoon klein. Daar word nietemin bereken dat ongeveer 1,000 noodlottige reaksies op penisillienbehandeling in 1957 in die Verenigde State van Amerika alleen plaasgevind het, en navorsingswerk in Denemarke het aangetoon dat 3 noodlottige reaksies per 10 miljoen inspuitings verwag kan word.

1. Oorsig deur O. Idsöe, R. R. Willcox (konsulterende geneeshere van die Wêreldgesondheidsorganisasie) en T. Guthe (hoof van die Afdeling vir Veneriese Siektes en Treponematose, Wêreldgesondheidsorganisasie, Geneve). Gepubliseer in die *Bulletin* van die Wêreldgesondheidsorganisie, Deel 19, No. 3, 1958.

than that involved in the use of many other drugs, and the tremendous good which penicillin is doing in curing diseases and preventing death should not be overlooked. Furthermore, simple precautions may prevent some of the serious consequences which now occur.

First of all, penicillin should not be used unless prescribed by a physician. In this connexion the WHO experts point out that severe penicillin reactions occur after repeated exposure to the drug, and that many cases of severe reactions can be attributed to previous unnecessary use of antibiotics.

Secondly, penicillin should not be used against minor infections for which it is ineffective, or not more effective than other drugs.

Thirdly, self-medication with antibiotics is dangerous and should be avoided. The addition of penicillin to toothpaste, chewing gum, etc. is 'indefensible.' Penicillin ointments should also be avoided.

Another reason for care in the use of penicillin is the development of resistance to antibiotics in staphylococci. These are among the most common micro-organisms and are found in the noses and throats of many healthy persons. Most strains of staphylococci were susceptible to penicillin when the drug first came into use, but hardy and more resistant strains emerged and have become a menace in hospitals where they sometimes cause deadly epidemics among children and infants.

According to the study, patients with a personal or family history of allergy are most likely to develop severe adverse penicillin reactions. In general, reactions are most common in adults between 20 and 49 years of age; they are rare in children under 12, and the frequency decreases rapidly with increasing age after 50.

PENICILLIN + ANTIHISTAMINES

There is one important practical and effective way in which the hazard of penicillin sensitivity may be tackled. As we have already pointed out,[2] the Council on Pharmacy and Chemistry of the American Medical Association has recognized the use of injectable antihistaminic drugs for prophylaxis against allergic reactions in the course of blood transfusions. This decision suggests a rational procedure which would increase the confidence with which the practitioner could administer antibiotics, provided a suitable antihistaminic drug was added to the penicillin preparation being used.

2. Editorial (1957): Med. Proc., **3**, 89.

Namate 'n steeds groter aantal mense meer en steeds meer penisillien gebruik, en geleidelik gevoelig vir hierdie antibioticum gemaak word, is dit moontlik dat ook die aantal toekomstige reaksies sal toeneem. Op die oomblik, egter, is die gevare verbonde aan die gebruik van penisillien nie groter as die gevare wat deur menige ander artsenymiddel meegebring word nie, en die geweldige waarde van penisillien by die genesing van siektes en die voorkoming van sterfgevalle moet nie oor die hoof gesien word nie. Temeer, eenvoudige voorsorgmaaatreëls is dikwels voldoende om baie van die ernstige reaksies wat vandag hul verskyning maak, te voorkom.

In die eerste plaas moet penisillien nie gebruik word tensy 'n geneesheer dit voorgeskryf het nie. In hierdie verband wys die deskundiges van die Wêreldgesondheidsorganisasie daarop dat ernstige penisillienreaksies plaasvind na herhaaldelike blootstelling aan die middel, en dat talle gevalle van ernstige reaksies toegeskryf moet word aan die vroeër onnodige gebruik van antibiotica.

In die tweede plaas moet penisillien nie gebruik word vir die behandeling van geringe infeksies waarvoor dit in elke geval nie doeltreffend, of nie meer doeltreffend as ander artsenymiddels is nie.

In die derde plaas is self-behandeling met antibiotica gevaarlik; dit moet derhalwe vermy word. Die byvoeging van penisillien by tandepasta, kougom, ens., is ‚onverdedigbaar.' Penisilliensalwe moet ook nie gebruik word nie.

Nog 'n rede vir versigtigheid by die gebruik van penisillien is die ontwikkeling van weerstand teen antibiotica by stafilokokke. Hulle ressorteer onder die mees gewone mikro-organismes, en word aangetref in die neus en keel van talle gesonde persone. Die meeste soorte stafilokokke is deur penisillien vernietig toe die middel vir die eerste keer gebruik is, maar meer geharde en weerstandskragtiger soorte het met verloop van tyd hul verskyning gemaak en 'n gevaar geword in hospitale waar hulle soms dodelike epidemies onder kinders en babetjies veroorsaak.

Volgens die deskundiges is dit waarskynlik dat ernstige nadelige penisillienreaksies hul verskyning sal maak veral by pasiënte met 'n persoonlike of familiegeskiedenis van allergie. Oor die algemeen word sodanige reaksies veral waargeneem by volwassenes tussen 20 en 49 jaar; hulle is 'n seldsame verskynsel by kinders onder 12, en die frekwensie daal vinnig nadat die ouderdom van 50 jaar bereik is.

PENISILLIEN + ANTIHISTAMIENMIDDELS

Daar is een belangrike, praktiese en doeltreffende manier om die probleem van penisilliengevoeligheid aan te pak. Soos ons reeds daarop gewys het,[2] het die Farmaseutiese en Skeikundige Raad van die Amerikaanse Mediese Vereniging reeds die gebruik van inspuitbare antihistamienmiddels vir profilakse teen allergiese reaksies in die loop van bloedoortappings goedgekeur. Hierdie beslissing suggereer 'n rasionale prosedure wat die vertroue van die genees-

2. Redaksioneel (1957): Med. Proc., **3**, 89.

Luippold[3] has shown that the incidence of penicillin reactions could be reduced in this way very substantially. He has pleaded for the wider use of this safety measure as a routine procedure, both in hospitals and in private practice.

It may be argued that the dosage of the antihistaminic drug may prevent reactions but not deaths. This may be so in many cases; but if penicillin deaths represent merely the lethal extreme of a spectrum of allergic reactions, deaths may well be prevented; or the practitioner may be given a few life-saving minutes in which he can employ additional resuscitative measures. He is no longer without some potent means whereby a tragedy may be averted.

Luippold[3] het aangetoon dat die voorkoms van penisillienreaksies op hierdie manier aansienlik verminder kan word. Hy bepleit dus die uitgebreider toepassing van hierdie veiligheidsmatreël as 'n roetine-prosedure, sowel in hospitale as in die private praktyk.

Daar kan miskien geredeneer word dat die gebruik van antihistamienmiddels reaksies sal voorkom, maar nie sterfgevalle nie. In baie gevalle kan dit waarskynlik waar wees; maar as penisilliensterfgevalle bloot die dodelike uiterste van 'n spektrum van allergiese reaksies verteenwoordig, kan dit miskien moontlik wees om sterfgevalle te voorkom; of 'n paar lewensreddende minute kan aan die geneesheer gegee word vir die toepassing van addisionele opwekkingsmaatreëls. Hy sal nie langer hoef klaar te kom sonder 'n kragtige middel om 'n tragedie af te weer nie.

THE PATHOGENESIS AND THERAPY OF HUMAN AMOEBIASIS

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At the present time there is no doubt that *Entamoeba histolytica* is or may become at any time a pathogenic parasite of Man and may cause a certain percentage of acute and chronic cases of amoebiasis. This parasitic amoeba has been studied in Man and in other animals and it has been grown in a variety of culture media, but never in pure culture in the complete absence of accompanying bacteria.

Infections with *E. histolytica* present many interesting and unsolved problems, with reference to the occurrence of clinical manifestations. The large majority of persons found infected with this parasite have no marked symptoms referable to the infection. A small number develop mild intestinal symptoms and a very small proportion develop severe amoebic dysentery. Although the incidence of amoebiasis varies in different parts of the United States, the frequency of amoebic infection of the bowel with hepatic complications is probably much greater than is commonly realized.

Surveys from all parts of the world have shown that among apparently healthy, normal persons, a varying percentage harbour *Entamoeba histolytica* in their intestinal tracts. The prevalence of the infection varies in different localities, but it is true that there exists throughout the entire world a great reservoir of amoebic infection in persons who seem normal, healthy and without apparent intestinal symptoms of the infection. With such a large reservoir of infected individuals, it is interesting that there is so little correlation between the incidence of these healthy carriers and the number of cases of acute amoebic dysentery in the subjects harbouring the parasite.

Another interesting question which has never been answered, concerns the symptomless carriers who develop acute amoebic dysentery: is the pathology due to the same strain of *E. histolytica* which had been present in the carrier state, or is the disease produced by a new infection or a different strain of the amoeba? If the pathology was due to the original strain, then we must conclude that there has been some change in the intestinal tract or in the amoeba which stimulated the parasite to produce massive tissue destruction.

Even though we now have a vast amount of information about the habits and life history of *Entamoeba histolytica,* there are still wide gaps in our knowledge of pathogenesis. One of our main questions is why are there far greater numbers of symptomless carriers who pass only cysts and who are apparently asymptomatic than there are cases of acute amoebic dysentery? This question of the symptomless carrier is one of peculiar difficulty. In 1913

3. Luippold, E. J. (1954): J. Med. Soc. New Jersey, **51,** 424.

3. Luippold, E. J. (1954): J. Med. Soc. New Jersey, **51,** 424.

Walker and Sellards (working in Manila, Philippine Islands) fed *Entamoeba histolytica* cysts from healthy carriers, some of whom had never had signs or symptoms of the infection, to 16 healthy volunteers. Fifteen of the 16 became infected with *E. histolytica,* but only 4 of the 15 subsequently developed acute amoebic dysentery. The specific explanation for these clinical and pathological variations is not known. It may be related to the parasite itself, to the condition of the host, to possible nutritional factors, to environmental influences of various kinds or to a combination of one or more of these factors.

One of the difficult questions to clarify is the condition of the mucosa in the symptomless carrier of *Entamoeba histolytica.* It has been found repeatedly that some amoebic ulceration of the large intestine of Man, and often amoebic liver abscess, may occur in individuals who have had no signs, symptoms or other evidence of amoebic infection. Are these cases of known amoebic infection in whom no ulceration is ever present? In an attempt to find some information on this point, Faust (1941) examined the intestinal tract of 202 persons within 4 hours after death by accident. Thirteen were found to harbour *E. histolytica* in the large intestine. In 7 of the 13 positives superficial lesions of varying extent were found. In 6 others no lesions could be found throughout the entire length of the large intestine. In 2 of the 6 infection was established by the finding of a single typical *E. histolytica* cyst in each case. This study indicates that there may be an extensive amoebic infection in the large intestine without any gross evidence of tissue pathology.

Frye and Meleney (1938) infected several Rhesus monkeys with a human strain of *E. histolytica* which had been found highly pathogenic for kittens. In one monkey the infection persisted for several months and trophozoites were always abundant in the stools, but there was no evidence of dysentery or of even mild tissue damage. The animal was sacrificed after several months of continuous observation and the entire intestine examined carefully. There were no gross lesions although numerous active trophozoites were found in all portions of the large intestine. Sections from numerous areas showed amoebae in the lumen, on the surface of the mucosa and in the crypts of the glands, but there was no penetration or evidence of damage to the adjacent epithelial cells. Another monkey infected with the same strain of *E. histolytica* became emaciated and appeared chronically ill several weeks after infection was established. There were numerous amoebae in the stools, but no frank dysentery. The animal was sacrificed a few weeks after becoming ill and several well-defined amoebic lesions were found in the area of the caecum. The animal also had far advanced pulmonary tuberculosis, which was the primary cause of the chronic illness. This seems to indicate that chronic illness and debility of any nature may break down the balance between host and parasite.

The pathogenicity of various strains of *E. histolytica* has been studied by many investigators. Meleney and Frye, over a 10-year period (1931-1941), studied the pathogenicity of a number of strains of *E. histolytica* in kittens. This work was planned with the dual purpose of comparing the severity of the lesions produced by the different strains and of observing the effect of continuous, prolonged cultivation *in vitro* on the pathogenecity of the strains. It was necessary to develop a practical method of studying the pathogenic activity of the various strains and to be able to compare each strain under uniform conditions.

In the pathogenicity studies all precautions were taken to prevent the introduction of new bacteria into the cultures. Interchanging the bacterial flora between our more pathogenic and less pathogenic strains had no apparent effect upon the pathogenic activity of the amoebae. It was found that variations of the suspending media employed in the inoculation of cultures of *E. histolytica* into kittens did affect the pathogenic activity of the amoebae. These controlled pathogenicity studies, using a standard number of experimental animals in each series, showed that there were differences in the ability of these strains to produce pathology in kittens and that this difference could be demonstrated and was constant over a period of years. It was also shown that with the strains of *E. histolytica* and kittens which we employed no strain proved to be non-pathogenic and only one of several strains showed a consistent decrease in pathogenic activity as a result of artificial cultivation.

The small and large race of *E. histolytica* have been considered by some to account for differences in clinical manifestations. Some consider the small race much less pathogenic than the large. Frye and Meleney (1938) established a small race of *E. histolytica* in

culture from a patient with mild gastro-intestinal tract symptoms and tested the pathogenicity of this strain in a series of kittens. Cultures of this strain were inoculated into 22 kittens and 5 became infected. The lesions in these animals were superficial, there being little tendency for the amoebae to penetrate deep into the tissues, as was true of almost all of the large strains of amoebae which were studied in kittens. It is not possible to transfer this information from the kitten directly to Man, but it does indicate that in infection with the small race of *E. histolytica* there may be only superficial lesions and that with infections with this type of amoebae in Man there would be no signs of symptoms of the disease.

In a recent report by Jones *et al.* (1955), evidence of a difference between the clinical manifestations in patients harbouring large and small race *E. histolytica* was presented. They studied 19 'apparently healthy' Egyptian employees for a period of 24 weeks before treatment was given. The patients were studied carefully and then treated. Post-treatment examinations were made again during a 24-week follow-up period, including a control group of patients with no infection. The findings in this controlled linear study of non-dysenteric and mild hepatic forms of amoebiasis in Egyptians were interpreted as clinical support for the concept of mild pathogenicity of the small race and for the concept that 'apparently healthy carriers' of either race may have mild signs and symptoms if followed serially over a long enough period of time.

PATHOGENESIS OF AMOEBIASIS

We are all aware of the fact that infection with *Entamoeba histolytica* presents many interesting problems regarding the occurrence of tissue pathology and the accompanying clinical manifestations of the disease. In order to understand the possibilities we must have a general understanding of the life history and other activities of this parasite.

Infection occurs by the introduction into the mouth of an uninfected host of a cyst or cysts. The cyst of *Entamoeba histolytica* passes unharmed through the stomach and into the small intestine. During its passage through the small intestine or after arrival in the caecum, the 4-nucleate amoeba within the cyst becomes active and emerges from the cyst.

After excystation, the normal 4-nucleated amoeba undergoes further nuclear division and single nuclei, with a portion of ectoplasm, separate into 8 small motile amoebae. This multiplication takes place in the lumen of the caecum. Here the amoebae grow to full size and then undergo mitotic and cellular division. The amoebae from the caecum may be carried in the fecal contents toward the terminal portion of the colon, undergoing encystation in preparation for survival outside the body until they are ingested by a new host. If conditions in the caecum or parts of the large intestine are favourable for tissue invasion, the motile amoebae may penetrate the wall of the intestine and produce lesions. The amoebae may produce tissue destruction on the surface of the mucosa; in the natural depressions or rugae; or in the lumen of the glands.

The penetration into the tissues may be accomplished by combined physical and chemical action. Amoeboid movement of the parasite may permit penetration between epithelial cells, or the lytic toxin of the amoebae may digest these cells before penetration into the deeper tissues takes place. Frequently the amoebae penetrate beneath the epithelial cells to the base of the glands and there multiply, outside the basement membrane, before progressing into the connective tissue stroma between the glands. From here they pass down toward the muscularis mucosae, causing oedema and necrosis of the tissue and dilatation, rupture or thrombosis of capillaries. Ultimately the necrosis involves the entire thickness of the mucosa. It may extend laterally over a wide area, or it may be sharply limited to a small group of glands. The amoebae in the fundi of the glands soon break through the basement membrane and penetrate the muscularis mucosae either through the tissue spaces or in the lymph or blood vessels.

In the submucosa the amoebae spread out in all directions between the connective tissue fibres. Their toxin causes oedema, fibrin formation and degeneration of cells and intercellular fibres. The submucosa often becomes several times its normal thickness. There is little or no cellular response on the part of the host to the amoebae, so that in early lesions before bacterial contamination few polymorphonuclear leucocytes and only a moderate number of monomuclear cells may be found. With progression of the lesions due to the amoebae the bacteria gain access to the tissues, followed by a marked polymorphonuclear response and the degenerating submucosal lesion takes on the appearance of a pyogenic abscess. At the periphery of such a lesion bacteria are usually absent, but

numerous amoebae are present in the advancing area of oedema and necrosis. The development of lesions in the submucosa leads to interference with the nutrition of the mucosa above it and to the formation of the typical ulcer with overhanging edges, with extrusion of blood, necrotic material and amoebae into the lumen of the intestine. Advancing beyond the area of necrosis, the amoebae in the submucosa may enter the lymph or blood vessels, or may penetrate into other layers of the intestinal wall. If they enter blood vessels, they are carried by the blood stream to the liver, where they may form emboli with necrosis of the capillary walls and with continued multiplication and necrosis there eventually forms an amoebic liver abscess.

The process that has been described represents the unobstructed development of the severest type of amoebic lesion in the large intestine of Man. The lesions are as a rule most numerous in the caecum, proximal ascending colon and the rectosigmoid region. As has been stated, we often find, in persons dying from other causes than amoebiasis, no gross evidence of amoebic lesions, but microscopic lesions may be found in tissue sections. In such lesions there may be no definite necrosis of the tissues. The glandular epithelium may be missing in small areas, but except for the presence of *E. histolytica* trophozoites there is little or no change in the surrounding tissue. Such a condition either represents the presence of a strain of *E. histolytica* of a low degree of pathogenicity or great resistance to the parasite on the part of the host. This is without question the condition that exists in some of the cases of amoebiasis that produce no clinical symptoms.

EXTRA-INTESTINAL AMOEBIASIS

Extra-intestinal lesions are metastatic, coming primarily from the intestinal lesions. These lesions in other parts of the body may develop in the absence of any intestinal symptoms of the infection. The most common and important of the complications of amoebiasis is amoebic hepatitis or amoebic abscess of the liver. The amoebae are transported from the intestinal lesions to the liver by way of the portal blood stream. With superficial localization of the amoebic liver abscess, its extension to the surface of the liver is the rule, and adhesion to the adjacent viscera or parietal peritoneum is common, often resulting in perforation or direct extension outside the liver. Although the incidence of amoebiasis varies in different areas, the frequency of amoebic infection of the bowel and its hepatic complications are probably much greater than is commonly realized.

The next most common site of extra-intestinal amoebiasis is the lung. Such lesions may occasionally be embolic in origin but are usually caused by direct extension of liver abscesses through the diaphragm. The abscess may rupture into the pleural or pericardial cavity, but more often the lung becomes adherent to the diaphragm and extension occurs directly into the lower lobe. With the advance of the amoebae into the lung, a localized pneumonia develops with rapid formation of an abscess. Such an abscess contains the material typical of amoebic lesions. At the periphery of the abscess is a pneumonic process, partly interstitial in character but mainly showing the alveoli filled with fibrin and amorphous material containing few cells. Numerous amoebae may be irregularly distributed in the alveoli and to a less extent in the interstitial tissue.

The lung abscess usually opens into a large bronchus, discharging in the sputum a brownish, mucoid material containing blood and amoebae. If there is a direct connection with the liver, the discharge is similar to that of a liver abscess.

Amoebic lesions of the skin and subcutaneous tissues are also frequently encountered. Such lesions may occur after surgical drainage of an amoebic liver abscess, after drainage of a ruptured appendix or ruptured ulcer of the colon, from a colostomy opening or from direct extension of rectal ulcers through the anus by way of a fistula. They would probably never occur if the primary condition was recognized as amoebic and drug treatment instituted.

Other extra-intestinal amoebic lesions have been reported, but these are extremely rare. Amoebic abscesses of the brain are usually secondary to liver and lung abscesses. Amoebic infections of the gall bladder and various areas of the genito-urinary tract have been described. When *E. histolytica* is found in these areas it is undoubtedly due to an extension from a primary site in the liver, in the case of the gall bladder, or from the colon in cases of genito-urinary tract involvement. These complications are extremely rare but must be kept in mind as a possibility in differential diagnosis.

DIAGNOSIS OF AMOEBIASIS

The laboratory diagnosis of amoebiasis is not particularly difficult if a few simple fundamental procedures are observed. The diagnosis of amoebiasis, as with other technical procedures, requires some knowledge of the biology of the parasite and broad experience in identification and differentiation of the non-pathogenic amoebae which may be found in the intestinal tract of Man.

The clinical diagnosis of intestinal amoebiasis is not difficult to confirm by laboratory techniques. Specific diagnosis rests essentially upon demonstration of either cysts or trophozoites of *Entamoeba histolytica*. Insofar as is practicable, the procedures designed to demonstrate this animal parasite should be exhausted before accepting a clinical or a therapeutic diagnosis of amoebiasis.

Swartzwelder (1952) points out that errors in the diagnosis of amoebiasis are of 3 kinds:

1. Failure, because of poor technique or inadequate search, to detect the organism in individuals who harbour the parasite;
2. Confusion of various non-parasitic objects in the stool or in sigmoidoscopic aspirate with *E. histolytica*; and
3. Confusion of other intestinal protozoa with this pathogen.

Sigmoidoscopic examination is a particularly valuable adjunct to stool examination, but this procedure has limitations. In a high percentage of patients with intestinal infection the lesions are beyond the range of this instrument and many cases of amoebiasis would be overlooked if this method of diagnosis were relied upon entirely for diagnosis. This would apply particularly to patients with lesions confined to the caecum, appendix and ascending colon, which are sites of frequent involvement without lesions being present in the lower portion of the large intestine.

The complement fixation test for amoebiasis has not yet been placed on a sufficiently dependable foundation for general use in diagnosis of amoebiasis.

THERAPY OF AMOEBIASIS

In our description of the life history and pathogenesis of *E. histolytica* it was pointed out that the trophozoites may live and multiply in the lumen of the intestine, in the wall of the bowel or in the tissues in other parts of the body. In the treatment of amoebiasis, the drugs to be used must be so selected that they exert their action in the right place. At present we have a number of drugs recommended for the treatment of amoebiasis, and various of these drugs have their individual proponents. There are only 2 effective systemic amoebicides, emetine and chloroquine. The other drugs act locally in the lumen of the intestine and are not effective in the elimination of the tissue parasites. With the introduction of the antibiotics, and particularly the broad-spectrum antibiotics, it was soon learned that they were effective in clearing a large proportion of lumen and tissue infections in the wall of the intestine; but the antibiotics are of no value in the prevention or treatment of extra-intestinal amoebiasis.

The drugs most successful for the control of amoebic infection are those having a sufficient margin of safety to permit their use without danger to the host and yet be capable of relieving the patient of symptoms and eradicating the causative agent, *Entamoeba histolytica*.

Table 1 shows the drugs now commonly used in the treatment of amoebiasis.

TABLE 1: AGENTS USED IN THE TREATMENT OF AMOEBIASIS

I. *Cephaeline alkaloida*:
1. Emetine hydrochloride.
2. Emetine bismuth iodine. (20% emetine—20% bismuth administered orally.)

II. *Halogenated Hydroxyquinolines*:
1. Chiniofon (Yatren-Anayodin) (28% iodine).
2. Diiodoquin (63.9% iodine).
3. Iodochlorohydroxyquine (Vioform) (37.5% iodine).

III. *Arsonic Acid Derivatives*:
1. Acetarsone (Stovarsol) (27.3% metallic arsenic).
2. Carbarsone (28.% metallic arsenic).
3. Thiocarbonate (Thioarsenite).
4. Bismuth glycolgarsamilate (Milibis). (15.01% metallic arsenic—41.88% metallic bismuth.)

IV. *4-Aminoquinolines*:
1. Chloroquine phosphate (Aralen *et al.*).
2. Diphosphate dihydrate (62% base) administered orally.
3. Hydrochloride (89% base) administered parenterally.

V. *Antibiotics*:
1. Terramycin.
2. Tetracyn.
3. Others.

The ideal amoebicide should be absorbed and distributed in its active form so that it is effective systematically against trophozoites in the tissues as well as against motile forms in the lumen of the intestine. Hargreaves (1945) reported that 57 patients with resistant amoebiasis showed marked improvement when treated with penicillin. He found that the temperature of these patients usually became normal within 24 hours. The stools in most instances became normal within 48 hours, but the amoebae were still present.

Shaffer and Frye (1948) showed that penicillin and streptomycin, alone or combined, in fairly high concentrations, when added to cultures of *E. histolytica*, had little if any effect on the growth and multiplication of the amoebae, but did inhibit growth of certain bacteria in the cultures. Armstrong, Wilmot and Elsdon-Dew (1949) observed partial or complete healing of amoebic ulcers, demonstrable by proctoscopic examination, following treatment with penicillin and Sulfasuxidine.

In contrast to penicillin and streptomycin, bacitracin (when added to cultures of *E. histolytica*) inhibited growth of the amoebae. Longacre (1948) treated several patients with amoebic colitis with bacitracin given orally. The amoebae disappeared from the stools, the lesions cleared rapidly and there was rapid clinical improvement.

Clinical successes using aureomycin in the treatment of amoebiasis was first reported by McVay and his associates in 1949. In 1950, Armstrong, Wilmot and Elsdon-Dew reported the use of aureomycin in acute cases of amoebic dysentery.

Terramycin was developed in 1950. Most and van Assendelft (1950) found Terramycin effective in the treatment of intestinal amoebiasis. Killough and Magill (1951) reported the treatment of 7 patients with amoebic dysentery with Terramycin. In all patients there was disappearance of bloody diarrhoea, tenesmus and other dysenteric symptoms within 2-6 days. Stools and proctoscopic specimens became negative for amoebae after 2 days in 4 patients. In one patient an amoebic abscess of the liver developed during Terramycin therapy.

Tobie *et al.* (1951) treated all occupants in separate buildings of a mental institution with bacitracin, aureomycin or Terramycin; a single drug was used in each building. Though all patients were asymptomatic before therapy, 49% harboured *E. histolytica*. Terramycin was found to be 100% effective in eliminating the organism from the intestinal tract on the basis of a 6-month follow-up, aureomycin was 60% effective and bacitracin only 28% effective after 2½ months of follow-up.

Armstrong, Wilmot and Elsdon-Dew (1950) treated 52 African cases of acute amoebic dysentery with aureomycin. This broad-spectrum antibiotic was given orally in doses of 0.25 g. 4 times daily at 6-hour intervals for 15 days. Sigmoidoscopy was done daily until all ulcers were healed. The authors considered the successes with aureomycin, after 20 days, as 94% against 50% successes with emetine. They were disappointed, however, with the 14% relapse rate among a small number of their 'successful' aureomycin-treated cases who were followed for an additional 4 weeks after discharge from the hospital. These same workers used 1 g. of Terramycin daily for 15 days in 49 acute cases of amoebic dysentery. At the end of 27 days there was success in 91.4% of cases treated. Two patients developed hepatitis which progressed in spite of continued Terramycin therapy and necessitated the use of emetine on the 16th day in one case and chloroquine on the 6th day in a second. They also used chloramphenicol, neomycin, streptomycin, bacitracin and certain combinations of antibiotics and other amoebicides. From these studies they concluded that Terramycin and aureomycin were very effective when used alone in acute amoebiasis.

Frye, Brooke and Weinstein (1952) gave a preliminary report of a comparative study of the efficacy of aureomycin, Terramycin and chloramphenicol against acute amoebic dysentery occurring in the United Nations prisoners of war in Korea in 1951. The criteria for acceptance in the amoebic dysentery study series were the presence of diarrhoeal disease with muco-sanguineous exudate in the stools, visualized enteric lesions and the presence of trophozoites of *E. histolytica*. No asymptomatic carriers were included in these studies. The same treatment schedule was used for all 3 antibiotics. Each patient received 2.0 g. of the antibiotics as a loading dose and then 0.5 g. every 6 hours for 10 days. After 10 days treatment was stopped and the patients followed for a period of 6 weeks. The results obtained with these 3 antibiotics are shown in Table 2. Terramycin in this group was the most effective with only 1 failure (or 97.5% effective), aureomycin was less effective with 12 failures (70.7% effective) and Chloromycetin was the least effective of the 3 broad-spectrum

TABLE 2: RESULTS OF TREATMENT OF ACUTE AMOEBIC DYSENTERY WITH 3 BROAD-SPECTRUM ANTIBIOTICS ASSESSED AT THE END OF 6 WEEKS

Therapy	*Number of Patients Treated*	*Success*		*Failure*	
		Number	*Per Cent.*	*Number*	*Per Cent.*
Terramycin	40	39	97.5	1	2.5
Aureomycin	41	29	70.7	12	29.3
Chloromycetin	39	21	53.8	18	46.2

From Frye, Brooke and Weinstein (1952): Ann. New York Acad. Sci., **53**, 1104.

antibiotics with 18 failures (53.8% effective). There were surprisingly few gastro-intestinal side reactions to these antibiotics among this group of patients.

Martin *et al.* (1953) reported on the complete study, in the prisoner-of-war camp, of the comparative efficacy of amoebicides and antibiotics in acute amoebic dysentery, used alone and in combination in 538 cases. Table 3 gives the results of this extensive study. Carbarsone, chiniofon, chloroquine and chloramphenicol used alone had minimal therapeutic effect in this disease. Emetine and aureomycin alone and the combination of bismuth glycolylarsenate and chloroquine diphosphate (Milibis^{R}-Aralen^{R}) gave a good initial response but a high relapse rate. Emetine, carbarsone and chiniofon combined gave an excellent initial response but a moderate relapse rate. Terramycin alone and in combination with other amoebicides and the combination of aureomycin and chloroquine diphosphate all gave excellent responses and low relapse rates.

Table 3 also shows the results obtained in a group of patients followed with only supportive therapy. At the termination of the follow-up period 11 of the 66 patients had no clinical or parasitological evidence of amoebic infection. These observations demonstrate that spontaneous recovery does occur and must be given consideration in the evaluation of any specific therapy.

McHardy and Frye (1954) reviewed the literature on the use of antibiotics in the management of amoebiasis. They found that of the broad-spectrum antibiotics Terramycin is the drug of choice in the management of amoebiasis. Fumagillin (Fumadil), a direct-acting antibiotic, because of its restricted bacterial spectrum, is an efficient amoebicidal substance. They also found that antibiotics were of no value as an amoebicide in the

TABLE 3: THERAPEUTIC RESPONSE IN 538 CASES OF ACUTE DYSENTERY ASSESSED AT THE END OF 6 WEEKS

Treatment Agent	*No. of Cases*	*Therapeutic Response*		*Failures Followed for 6 Weeks*			
		Success	*Failure*	*Number Re-treated before 6 Weeks*	*Number with E. histolytica in Stools at 6 Weeks*	*Number Clinically Ill.*	*Number with Active Colitis Sigmoidoscopically*
Standard Amoebicides							
Emetine	22	10	12	2	10	1	1
Carbarsone	22	4	18	12	6	2	3
Chiniofon	24	9	15	6	9	1	1
Chloroquine	31	13	18	5	13	6	5
Emetine, Carbarsone and Chiniofon	23	19	4	0	4	0	0
Milibis-Aralen	22	11	11	4	7	3	0
Antibiotics							
Terramycin	104	98	6	3	3	2	3
Aureomycin	41	31	10	3	7	4	2
Chloramphenicol	41	11	30	9	21	10	13
Antibiotics and Amoebicides Combined							
Terramycin and standard amoebicides for 10 days	97	93	4	2	2	1	1
Terramycin and chloroquine for 5 days	22	20	2	1	1	1	1
Aureomycin and chloroquine for 10 days	23	23	0	0	0	0	0
Supportive Therapy							
Bed rest and nutritional supplements	66	11	55	39	16	8	11

From Martin, Garfinkel, Brooke, Weinstein and Frye (1953): J. Amer. Med. Assoc., **151,** 1055.

treatment of extra-colonic amoebic involvements.

In a recent study Sappenfield *et al.* (1953) used Terramycin and Fumagillin in the treatment of a large group involved in a waterborne outbreak of amoebiasis. The epidemic was confined to the employees of a woodworking plant. Stool specimens were obtained from all the employees and examined for *E. histolytica* and other intestinal parasites. The examinations were repeated on each individual until a diagnosis of amoebiasis was made or until 4 negative specimens had been submitted. Table 4 shows the results of the diagnostic programme. There were no gross signs or clinical symptoms in any of the individuals harbouring *E. histolytica* and all were working regularly. A mass treatment programme was arranged in the plant with the approval of all concerned, including the individual, the private physician, the local medical society, plant management, the union and the Health Department. A treatment schedule was arranged so that one half the daily medication was given in the morning in a treatment centre set up in the plant. The other half of the daily dose was given to the patient each day to take just before leaving the plant at the close of the work day.

TABLE 4: RESULTS OF SOUTH BEND DIAGNOSTIC PROGRAMME

Number of plant employees	1,561
Number of employees interviewed	1,548
Employees contributing specimens	1,542
Percentage of employees harbouring *Entamoeba histolytica*	52.4

Infected individuals were treated with Fumagillin, 20 mg. twice daily for 10 days, or Terramycin, 1 g. twice daily for 10 days. The type of treatment to be given to each individual was decided by alternately selecting cases as they arrived for their first day of therapy. A total of 805 employees reported for treatment. Terramycin was given to 405 and Fumagillin to 400. After a complete analysis of the records, 714 employees had fulfilled one of the following criteria and were included in the final evaluation:

1. A positive stool examination after completion of treatment or

2. Four negative stool examinations over a 3 to 4-month follow-up period after completion of treatment of the 714 patients meeting these requirements.

Three hundred and fifty-eight received Terramycin and 356 received Fumagillin.

The results of therapy with these 2 antibiotics are shown in Table 5. After one course of therapy with Terramycin, 338 (94.4%) were negative. Of those treated with Fumagillin 334 (93.4%) were negative at the end of the follow-up period. There were 42 patients still positive after the first course of therapy. Each of these patients was treated again, this time with the alternate drug. Four of the 20 patients remaining positive after the original Fumagillin therapy were still positive after re-treatment with Terramycin. Two of 13 patients remained positive after re-treatment with Fumagillin.

This study reconfirmed that Terramycin is an effective agent in the treatment of asymptomatic amoebiasis, and that Fumagillin was equally effective in the same group of individuals, but that the side reactions were more severe. This type of infection with *E. histolytica*, or with mild symptoms, is the usual type of infection seen by practising physicians in the United States. As has been mentioned, extra-intestinal amoebiasis is not eliminated or prevented with the broad-spectrum antibiotics. It has now been over 2 years since this treatment programme was completed and there have been no reports of liver abscess or other extra-intestinal amoebiasis in the 805 employees diagnosed and treated.

TABLE 5: RESULTS OF SOUTH BEND TREATMENT PROGRAMME

	First Course of Treatment			*Second Course of Treatment*					
		Post Treatment			*Post Treatment*		*Total*	*Total*	*Negative*
	Number Treated	*Stool Examination Negative*	*Positive*	*Number Treated*	*Stool Examination Negative*	*Positive*	*Treated*	*No.*	*Per Cent*
Terramycin	358	338	20	20*	16	4	378	354	93.7
Fumagillin	356	334	22	13**	11	2	369	345	93.5
	714	672	42	33	27	6	747	699	

* Treated previously with Fumagillin. The other 2 were followed by private physicians.
** Treated perviously with Terramycin. The other 7 were followed by private physicians.

During the past year Frye (1955),* in unpublished studies in a large mental institution, has used several of the new amoebicides and antibiotics. Table 6 gives some preliminary results of this study. Tetracyn has given results equal to those obtained with Terramycin in the treatment of asymptomatic intestinal amoebiasis. Stylomycin* has also been found effective in asymptomatic carrier cases and there have been no side reactions to this antibiotic in the dosages used. Larger doses than those shown in Table 6 are now being used and we have had no untoward reactions to date.

TABLE 6: THE EFFICACY OF TETRACYN AND STYLOMYCIN AGAINST ASYMPTOMATIC AMOEBIASIS

Number Patients Positive for E. histolytica	*Antibiotic Therapy*	*Dosage*	*Unfavorable Reactions To Therapy*	*Therapeutic Response (Two Months' Follow-up)*	
				Success	*Failure*
33	Stylomycin	500 mg. daily—6 days	None	29	5
34	Tetracyn	2 g. daily —6 days	None	31	3

TREATMENT OF EXTRA-INTESTINAL AMOEBIASIS

The standard therapy of amoebic hepatitis and amoebic abscess of the liver until recently consisted of emetine injections alone or combined with aspiration of the contents of the abscess. Before antibiotic therapy, to control secondary bacterial infection, open drainage of the abscess increased the mortality rate. The emetine treatment of amoebic hepatitis and liver abscess is usually successful, but a less toxic drug has been needed for the treatment of extra-intestinal amoebiasis. Conan (1948) was the first to use chloroquine against amoebic hepatitis. He shrewdly combined the observations that chloroquine is found in high concentrations in the liver when administered by mouth and that it was effective against the malarial protozoan. With this information he tested the action of chloroquine against *E. histolytica in vitro* and showed this drug to be active against the trophozoites. Since Conan's first report a large number of patients with amoebic hepatitis and hepatic abscess have been treated with chloroquine and the results have been uniformly good.

Frye *et al.*, in unpublished data, treated 9 cases of amoebic hepatitis with chloroquine. Three of the 9 had a definite liver abscess. Five received chloroquine alone with excellent therapeutic results. One case had some persisting symptoms while on chloroquine, but progressed to complete recovery when Terramycin was added. Two cases of liver abscess were treated with chloroquine and Terramycin and one with chloroquine and emetine. Though there was improvement in all 3 on drug therapy, complete recovery was delayed until the abscesses were drained. From these studies it was concluded that chloroquine is a highly effective therapeutic agent in the treatment of amoebic hepatitis.

Conan originally used a priming dose of 0.3 g. of the base twice daily for 2 days and a sustaining dose of 0.3 g. daily for 12 days. Chloroquine diphosphate (Aralen) is the form available on the market at present and the dose is 0.5 g. twice daily for 12 days. Chloroquine has been successful in hepatic infections which emetine failed to cure; likewise, chloroquine failures should be treated with emetine.

Although emetine has been used successfully in the treatment of skin amoebiasis, there have been no reports to date of the use of chloroquine in such cases. The fact that chloroquine is concentrated far more greatly in the liver than in other tissues might mean that it would not be effective in extra-intestinal amoebiasis other than in the liver.

DISCUSSION

In this presentation attention has been called to some of the unsolved problems in human amoebiasis. We are still unable to explain why *Entamoeba histolytica* produces severe tissue damage in some circumstances and no damage at all in others. Asymptomatic carrier cases occur far more commonly than infections with definite signs and symptoms of infection with *E. histolytica.* Pathogenicity studies have shown that there is a difference between certain strains of *E. histolytica* when studied in experimental animals. There is also some clinical evidence that the small race produces fewer clinical manifestations in humans, when patients are followed over a long period time, than does the large race.

A review of the life cycle and the pathogenesis of *E. histolytica* has been described in

* The following drugs were supplied by the makers for use in this study: Tetracyn by Charles Pfizer and Co., Brooklyn, N.Y., and Stylomycin by Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N.Y.

an attempt to get a better understanding of the problems involved in therapy. The site of action of an amoebicide in the acute case of amoebic dysentery and in the asymptomatic carrier, or in the extra-intestinal infection, must be understood if successful therapy is to be expected. On the basis of present knowledge, all infections in Man with *Entamoeba histolytica* should be treated.

The evaluation of anti-amoebic drugs and the comparative effectiveness in each case present a number of problems. The response to therapy in cases of acute amoebic dysentery is quite different from those patients with mild symptoms or in the asymptomatic carrier.

The length of time that the patients are followed after completion of therapy is very important, as many drugs seem to produce an apparent cure for several days or weeks; yet when the patient is examined severals weeks later, a high rate of parasitological and clinical relapse is found. Stool examination technique and careful follow-up procedures also have a considerable bearing on apparent cure rate. The laboratory diagnosis of amoebiasis is not particularly difficult, but as with any other diagnostic procedure, it requires some knowledge and experience. Specific diagnosis rests essentially upon demonstration of either the cysts or trophozoites of *Entamoeba histolytica.*

In the treatment of acute amoebic dysentery, we are faced with the need for prompt relief of symptoms as well as the complete eradication of the parasite. In mild and asymptomatic cases the treatment would seem to be much simpler. Here we have little or no tissue pathology in the intestinal tract, but the parasite must be eliminated from both the tissue and the lumen. Although emetine has been used for over 40 years in the treatment of amoebic dysentery (and for a number of years it was the only amoebicide available) one must remember that it is a toxic drug. The cure rate with this drug and with all other amoebicides now in use varies considerably.

During the past few years a number of antibiotics have proved to be of considerable value in the treatment of all forms of intestinal amoebiasis. In the hands of a large group of investigators Terramycin has been found to be the most effective in eliminating the parasite from the tissues and from the lumen of the large intestine. Of the broad-spectrum antibiotics now in use, Terramycin is the drug of choice in the management of intestinal amoebiasis.

It must be emphasized here that the antibiotics have no apparent effect on extra-intestinal amoebiasis; in fact, amoebic abscesses of the liver have developed in patients while on antibiotics, and in whom the intestinal involvement had been cured. The treatment of choice in hepatic amoebiasis is now chloroquine diphosphate. In certain cases emetine may be necessary if chloroquine fails. For other types of extra-intestinal infection with *E. histolytica* emetine must still be considered the drug of choice due to lack of information on the use of chloroquine in the treatment of extra-intestinal amoebiasis other than in cases of hepatic involvement.

OPSOMMING

'n Paar van die onopgeloste probleme van amebiase by die mens word in oënskou geneem. Ons is nog nie in staat om te verduidelik waarom *Entamoeba histolytica* in sommige omstandighede ernstige weefselbeskadiging tot gevolg het, en in ander gevalle glad geen skade veroorsaak nie. Asimptomatiese draergevalle kom veel meer dikwels voor as infeksies met definitiewe tekens en simptome van infeksie met *E. histolytica.* Patogeniteitstudies het aan die lig gebring dat daar 'n verskil tussen sekere soorte *E. histolytica* is wanneer hulle by proefdiere bestudeer word. Daar is ook kliniese bewyse wat aandui dat die klein soort minder kliniese manifestasies by die mens veroorsaak, wanneer pasiënte oor 'n lang tydperk waargeneem word, as die groot soort.

In Oorslag van die lewenskringloop en die patogenese van *E. histolytica* word verstrek in 'n poging om 'n beter begrip te verkry van die probleme wat deur terapie teweeggebring word. Die plek van bedrywigheid van 'n amebevernietiger in 'n akute geval van amebiese disenterie en by die asimptomatiese draer, of in 'n geval van buite-ingewandsinfeksie, moet begryp word indien geslaagde terapie verwag word. Geoordeel aan die hand van die kennis waaroor ons op die oomblik beskik, moet alle *Entamoeba histolytica*-infeksies van die mens behandel word.

Die bepaling van die waarde van anti-amebiese middels en die vergelykende doeltreffendheid in elke geval lewer 'n aantal probleme op. Die reaksie op terapie in gevalle van akute amebiese disenterie is heeltemal verskillend van dié wat waargeneem word by pasiënte met ligte simptome, of by die asimptomatiese draer.

Hoe lank die pasiënt onder toesig gehou word ná voltooiing van die terapie is van groot belang want daar is etlike middels wat 'n skynbare genesing vir tydperke van etlike daes of etlike weke teweegbring, maar wanneer die pasiënt 'n hele paar weke later ondersoek word, word 'n hoë mate van parasitologiese en kliniese agteruitgang ontdek. Die tegniek i.v.m. die ondersoek van die ontlasting, en sorgvuldige opvolgingsprosedures oefen ook groot invloed uit op die skynbare genesingsyfer. Die laboratoriumdiagnose van amebiase is nie besonder moeilik nie, maar, net soos in die geval van ander diagnostiese prosedures, is kennis en ondervinding daarvoor nodig. Spesifieke diagnose berus essensieel op die demonstrasie van òf die cystes òf die trofosoïete van *Entamoeba histolytica.*

By die behandeling van akute amebiese disenterie is dit noodsaaklik om die simptome vinnig te verlig sowel as om die parasiet volkome uit te roei. Dit

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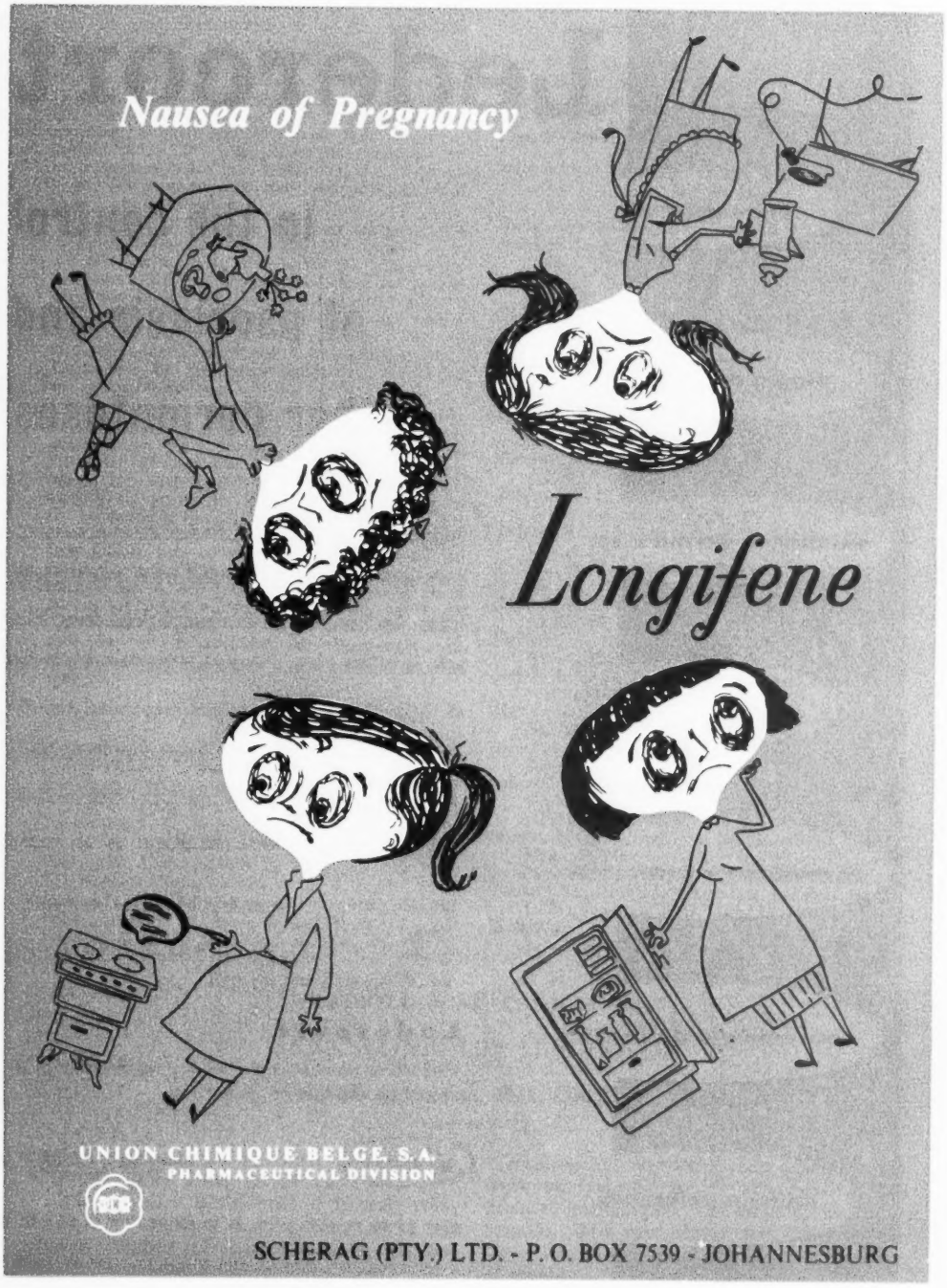
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skyn asof die behandeling van ligte en asimptomatiese gevalle heelwat eenvoudiger is. Hier het ons min of geen weefselpatologie in die ingewandskanaal nie, maar die parasiet moet uit sowel die weefsel as die buisholte verwyder word. Hoewel emetien meer as 40 jaar lank vir die behandeling van amebiese disenterie gebruik is ('n aantal jare lank was dit trouens die enigste beskikbare amebevernietiger), moet ons in gedagte hou dat dit 'n giftige middel is. Die persentasie genesings wat teweeggebring word met hierdie middel en al die ander amebevernietigers wat tans gebruik word, verskil nogal aansienlik.

Gedurende die afgelope paar jaar het geblyk dat 'n aantal antibiotica van aansienlike waarde is by die behandeling van alle vorms van ingewandsamebiase. 'n Groot groep ondersoekers het byvoorbeeld gevind dat Terramycin die doeltreffendste is vir die verwydering van die parasiet uit die weefsel en uit die buisholte van die dikderm. Van die breëspektrum-antibiotica wat tans gebruik word, is Terramycin die verkieslike middel vir die beheer as ingewandsamebiase.

Daar moet egter benadruk word dat die antibiotica skynbaar geen effek op buite-ingewandsamebiase het nie. Trouens, amebiase absesse van die lewer het ontwikkel by pasiënte wat met antibiotica behandel is ondanks die feit dat die ingewandskwaal genees is. Die verkieslike middel by die behandeling van amebiase van die lewer is tans chloorchindifosfaat. In sekere gevalle waar chloorchin misluk het, sal dit miskien nodig wees om emetien te gebruik. Vir ander tipes buite-ingewandsinfeksie met *E. bistolytica* moet emetien nog steeds as die verkieslike middel beskou word, weens die gebrek aan inligting oor die gebruik van chloorchin by die behandeling van buite-ingewandsamebiase, behalwe in gevalle waar die lewer aangetas is.

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RADIOLOGICAL CASE BOOK

GRANULOMA OF THE COLON

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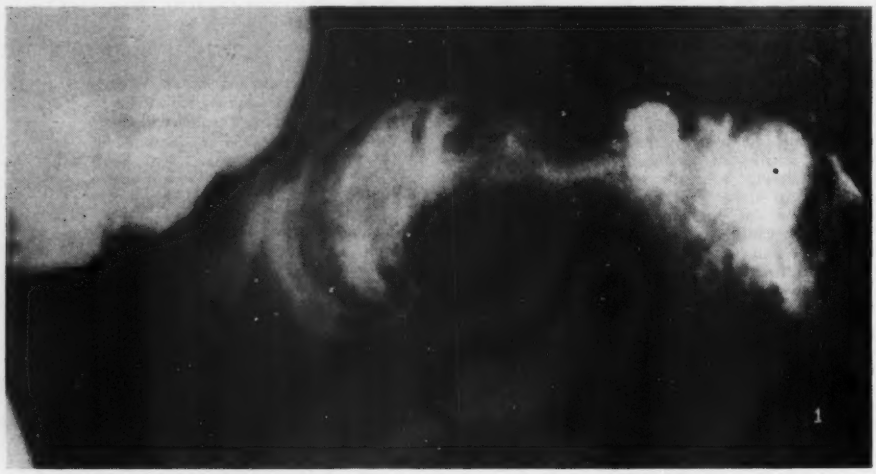
Johannesburg

Fig. 1 illustrates an infrequent cause of an intrinsic filling defect in the colon.

The patient, a White male of 50 years, complained of constant nagging pain in the left lower abdomen (of about 3 months' duration) and of rectal bleeding.

Examination revealed a mild anaemia. No mass was palpable in the abdomen and the physical examination was negative in other respects. His past history was non-contributory. The blood picture was that of secondary anaemia.

He was referred for colonic study by barium enema, as a diagnosis of carcinoma of the colon was entertained. This examination revealed a nodular filling defect, 4 × 2 cm., located on the inferior wall of the iliac portion of the sigmoid colon. There was no obstruction.



The features are those of a small carcinoma of the colon, except for the presence of a small, rather poorly defined, constant density within the nodular defect. This density was difficult to explain pre-operatively and it was tentatively considered to be an opaque, ingested fragment caught on the irregular neoplasm.

Surgery and subsequent section of the specimen showed the lesion to be a non-specific granulomatous reaction to a chicken bone transfixing the colonic wall.

OPSOMMING

'n Buitengewone oorsaak van 'n vuldefek in die dikderm word deur hierdie geval toegelig.

Die kenmerke was soos dié van 'n klein karsinoom, met uitsondering van die aanwesigheid van 'n sleggedefinieerde, konstante digtheid binne die knopdefek, soos radiologies gesien.

Daar is gemeen dat hierdie defek te wyte was aan 'n ondeurskynende, ingeneemde fragment, vasgevang op die onreëlmatige neoplasme.

Chirurgie en latere ondersoek van die monster het aangetoon dat die letsel 'n nie-spesifieke granuloomreaksie was op 'n hoenderbeen wat die wand van die dikderm deurboor het.

THREE BREAST CONDITIONS

WHICH REQUIRE CLARIFICATION

2. FISTULAE OF LACTIFEROUS DUCTS

A. LEE MCGREGOR, M.CH. (EDIN.), F.R.C.S. (ENG.)*
Johannesburg

Fistula of a milk duct is a condition which, though not very common, is seen often enough to come within the purview of every general practitioner, gynaecologist and surgeon. This lesion illustrates well that failure to appreciate the pathology leads to the perpetuation of a readily curable condition and to much unnecessary discomfort and morbidity.

In one of my cases abscesses had occurred near the areola intermittently for 10 years and I failed to realize the nature of the malady. I saw 5 other cases and still remained ignorant of the basic cause. In 1955 Atkins[1] described 'mammillary fistula' and the whole picture became clear. He pointed out that credit for

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the recognition of the true nature of the condition belongs to Zuska, Crile and Ayres[2] who described it in 1951 and pointed out the similarity of lactiferous duct fistula to fistula-in-ano.

The account of the condition given here is taken from the writings of the aforementioned workers. A résumé will also be given of 6 of my own cases, in none of which was the true nature of the lesion appreciated.

DEFINITION

A lactiferous duct fistula presents as a discharging sinus which opens on or just lateral to the edge of the areola on one or both breasts. There may be, and usually is, a history of healing and recurrence which may go back for many years. The condition occurs in females and has been seen between the ages of 15 and 63.

PATHOLOGY

The essential cause of the lesion is a blocking of the opening of one of the milk ducts on the surface of the nipple. The insensible duct secretions are so slight that they are not noticed, but if they fail to find their way to the exterior for any cause, they are pent up and dilate the duct in its ampullary part. Sometimes a distinct swelling may be seen on the areola. More usually the secretions burst their way through to the surface about the edge of the areola. Doubtless on occasions they escape through the opening of the duct on the nipple. The accumulation is made up of cast off keratinized squamous epithelium from the lining of the duct. Infection complicates the matter and a small abscess forms, bursts and a fistula results. After a variable time, and with or without treatment, the fistula heals only to recur again. This cycle may be repeated many times unless the cause is appreciated and removed.

Kilgore and Fleming[3] first drew attention to the frequent association of lactiferous duct fistula with indrawn nipples. Obviously duct obstruction may occur if the surface of the nipple is obstructed. It may also happen that an injury to the nipple may cause swelling and obstruction which may set the process going. The nipple may remain congenitally inverted or may become so in carcinoma and fibro-adenosis. Only one of Atkins' cases was associated with carcinoma of the breast and none of the 68 cases of Kilgore and Fleming.

This association, though rare, indicates the need for investigation of the tissue removed at operation. Zuska *et al.* described the changes in the duct following obstruction of its outlet by secretions. The duct is dilated especially in the ampullary area with secretions which are infected. A local subareolar abscess forms which bursts through the skin. There is spread of the inflammation to the periductal tissue. In old cases there may be much scarring and the fistulous track may be lined with a pyogenic membrane (Fig. 1).

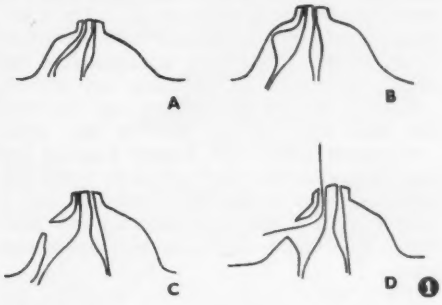


Fig. 1.
A: Two lactiferous ducts with ampullae are shown.
B. One duct is blocked and the ampulla is distended.
C. The abscess has burst through the skin forming a lactiferous fistula.
D. A probe has been threaded from the fistulous opening through the related duct.

CLINICAL PRESENTATION

The patient may present with a linear swelling beneath the areola, which is warm and tender, as happened in Cases 2 and 3. More usually she comes because of a sinus which is discharging pus.

The following personal cases are briefly recorded to illustrate the manner of clinical behaviour.

Case 1. Mrs. E. F., age 31, was seen in February 1946.

This lady, whose youngest child was 7 years old, presented with the story that 6 months before she had noticed a 'pimple' just outside the left areola. This formed a blister which burst. This had healed but it had repeatedly recurred with the spurting out of pus. The history was further not important.

The condition found on examination was a red patch just lateral to the left areola. There was a central scab. When this was removed, a probe extended for 1 inch towards the nipple and thick pus exuded from the opening on

the skin. The advice given to the doctor was to remove the wall of the abscess and to allow it to granulate from the bottom, the pus and tissue removed to be examined and antibiotics given. The doctor was advised to give the caution that permanent healing could not be assured.

Case 2. Miss J. B., age 15, a scholar, was seen in November 1952.

Three months before she had been punched on the left breast by a child. Three days before I saw her the left breast was swollen and ached and an abscess had burst over the areola, which was discharging pus. There was some surrounding induration and *retraction of the nipple.* There were small glands in the axilla. Treatment by penicillin was advised.

Case 3. Mrs. C. W. married, age 36, with one child aged 13, was seen in May 1947.

A month before this woman knocked her right breast with a bolt of cloth. She felt something was wrong there and had had a burning pain in the nipple area for two days. Apart from mild dyspepsia her health was good.

There was a raised, red, hot area over the right areola at 5 o'clock, with induration round the nipple. The area was tender. There were no axillary glands. The patient was referred to a general practitioner for treatment of a chronic subareolar abscess.

The subsequent history is as follows:

She developed single subareolar abscesses on the right or left or both sides innumerable times. There was never more than one on each side. The abscesses had burst at the outer border of the areola. In 1949 she could tolerate this no longer and asked her doctor what could be done surgically to cure here. He removed the nipple and areola on both sides. This cured the condition and up to this time, i.e. 9 years, there has been no recurrence.

Case 4. Mrs. H. J., age 37, 2 para (youngest child 8 months), was seen in September 1948.

In August 1947 her right breast became sore. In October 1948 a surgeon drained an abscess just lateral to the areola. Though the scar was healed, further abscesses had formed and burst repeatedly next to the areola.

There was a scarred thickened area lateral to the areola with a discharging sinus. The doctor was advised to make a wide resection of all diseased tissues. Again the relatives were told that recurrence was possible.

Case 5. Mrs. S. M. V., age 35, no children, was first seen in March 1950.

Her right breast had been removed 4 years before for 'cancer.' No malignancy was found. Five months before I saw her in March 1950 a small 'lump' was removed near her left nipple. The wound had opened, discharged pus, and healed repeatedly since.

Examination showed a discharging sinus just outside the left areola. Conservative treatment was advised.

Case 6. Mrs. J. B., age 32, was seen in November 1952.

Ten years ago this patient developed a hard lump in the central area of the left breast, which discharged blood and pus from the nipple. This recurred several times within the next 2 years.

She had a baby in 1946 and another in 1949 and was well between the births. After the second birth only blood was found by suction in the left breast and no milk.

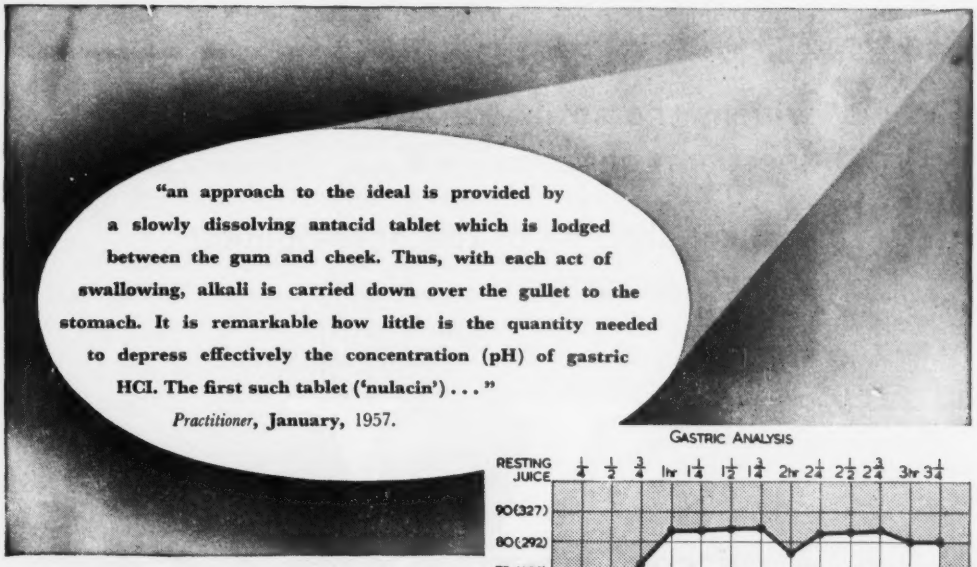
The right breast became infected a month later, and cleared with penicillin. A year later a small abscess opened just without the right areola. Six months later an abscess occurred on the left which was opened and cleared up but after 6 months it recurred. Meanwhile a succession of small abscesses continued on the right.

When I first saw her in November 1952 there was a discharging sinus just to the right of each areola. There was some local pain. She had been treated with antibiotics. Her health and bodily functions were otherwise normal.

There was a sinus opening to the right of each areola. No axillary glands could be felt. The doctor referring the case was told that there was a chronic duct infection present, and that the prognosis for cure was poor. Treatment advised was to continue the search for the appropriate antibiotic and to excise both sinus tracks.

The histories reported here indicate the behaviour of cases of lactiferous duct fistulae. They also show that 'as is your pathology, so is your practice.'

It was thought that there was an underlying chronic duct infection present to account for the chronicity. The cause of this was unexplained. In retrospect it is apparent that the situation of the external openings of the fistulae always in relation to the areola should have indicated a common pathology. In none of these cases did the treatment advised get at the root of the trouble. Only in Case 3, (Mrs. C. W.) did the general practitioner cure the patient by removing nipples and areolae —a sacrifice which is unnecessary now that the pathology is understood.



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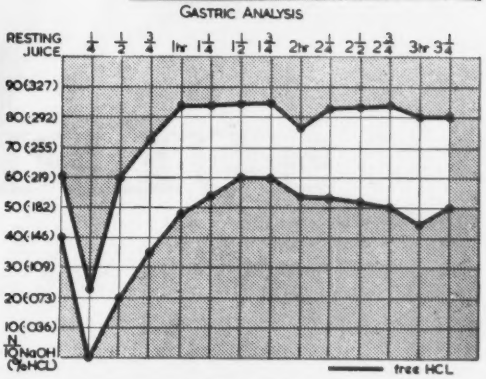

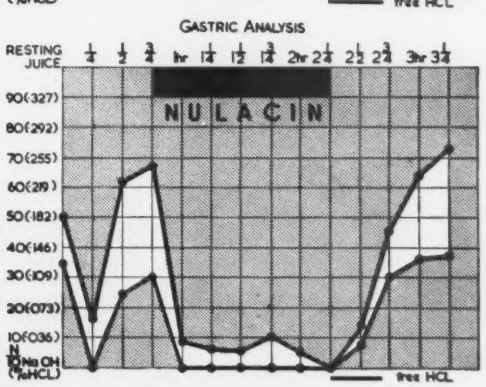

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59

TREATMENT

This is surgical. A lachrymal probe is passed into the fistulous opening. A little manipulation will cause its emergence on to the nipple through the affected duct. The probe is cut on to and the duct is laid open and the track cut away and saucerized. It is unnecessary to remove the proximal (nipple) part of the duct (Fig. 2).

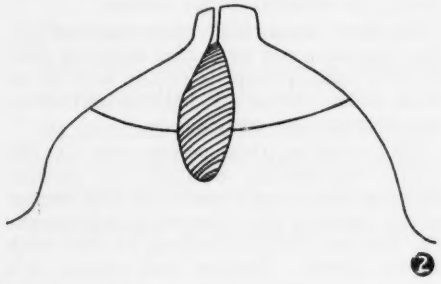

Fig. 2.
Diagram showing (shaded area) the fistulous area excised over the skin of the breast areola.

The wound is loosely packed with gauze plugging soaked in Eusol. Dressings are done daily, the aim being to secure healing from the bottom. It is wise that the patient be in a nursing institution for some weeks. When discharged she returns for daily dressings until healing is complete—a period of about 6 weeks.

SUMMARY

1. Lactiferous duct fistula is not rare.
2. It is due to blockage of a lactiferous duct by pent up secretions or by duct obstruction in inversion of the nipple.
3. Treatment is simple and effective if the pathology is understood and the fistulous track laid open and allowed to heal from the bottom.

OPSOMMING

1. Melkvoerende buisfistels is geen seldsame verskynsel nie.
2. Dit moet toegeskryf word aan die verstopping van die melkvoerende buis deur opgehoopte afskeidings, of aan buisobstruksie deur omstulping van die tepel.
3. Die behandeling is eenvoudig en doeltreffend as die patologie begryp en die fistelbaan oopgelê en toegelaat word om van onder af te genees.

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ELECTROENCEPHALOGRAPHY AT THE JOHANNESBURG HOSPITAL

IN VIEW OF A REPORT BY THE INTERNATIONAL FEDERATION OF SOCIETIES FOR ELECTROENCEPHALOGRAPHY

M. K. WRIGHT, M.Sc., M.B., B.Ch.*
Johannesburg

The publication of the recommendations of the International Federation of Electroencephalographic Societies[1] relating to most topics of organization of an EEG Department seems a fit time to compare their recommendations with the conditions prevailing at the Johannesburg Hospital. In most particulars, the EEG Societies' proposals are not pipe-dreams; they describe more or less established practice overseas and they are intended for those setting up new EEG Departments. The standardization in minor matters of procedure is a far lesser objective.

In the present state of electronic technology, there is no reason to use electroencephalographic apparatus that falls below the required standard in any major particular. Therefore some of the important performance figures recommended by the EEG Societies as a minimum are given, with corresponding data in parentheses for the apparatus that records half, if not more, of the electroencephalograms recorded at the Johannesburg General Hospital's EEG Department.

The longest time constant should be at least 0.3 second (the hospital instrument has a maxi-

* Formerly Registrar and Neurophysiologist to the Department of Applied Electrophysiology, The National Hospital for Nervous Diseases, Queen Square, London.

mum time constant computed at 0.005 second, while it is generally operated at a much more brief setting): at time constant settings below, i.e. less in time, 0.3 second most of the diagnostically important slow cerebral waves are, if present in a particular subject, imperceptible in the EEG. Further, after high voltage transients, spurious slow waves appear in the EEG if the time constant of the amplifiers is too brief.[2] A calibrator signal applied to each channel of a multi-channel machine simultaneously, as well as a time trace on the record to check any variations in speed of the paper drive mechanism, are both essential. (Neither devices are in operation at the local hospital unit). It is thus impossible to check if the same cerebral activity recorded by several channels would reproduce a similar graph upon the recording paper after amplification by the various channel amplifiers that must remain in part 'unknown quantities;' likewise, if the paper speed should vary (as it well may), there would be no way of telling if the duration, and hence the frequency, of brain potentials had been recorded accurately and constantly. (Certain gross dissimilarities between traces from different channels into which identical signals have been fed in the case of the hospital instrument under discussion are due to non-linearities which, to my knowledge, have not been analysed because the technical data simply are not available). The EEG Societies state that all writing points of the pen recorder styli should lie within 0.5 mm. of a line drawn vertically at right angles to the edge of the recording paper. (In hospital records that I have seen, such has never been the case). Pen recorder response should be linear within a close tolerance, while alteration of the setting of any one control should not change the amplifier characteristics governed by any other control by more than 5%. (This is not the case with the particular instrument under discussion). Further details could be supplied from experience during a stay of 13 months in charge of the EEG Department at the hospital, during which period upwards of 1,500 records were taken on this machine alone; prolonged criticism on this topic would, I believe, serve no further useful purpose.

The foregoing criticisms are not petty, for the standard of electroencephalography on the Witwatersrand suffers immeasurably and directly as a result of the technical shortcomings enumerated. The finer points of EEG diagnosis, I believe, are frustrated by this non-human element. To the same reasons, in part, is attributable the plain fact that in many other countries electroencephalography is esteemed as a diagnostic technique both reliable in many instances and also kind to the patients' dislike of pain as well as to their pocket, while the same is not altogether true of South Africa. Further, even if training courses were held here, an improper machine would detract from the value of tuition given on the basis of its records. Apparently no one can at present remedy the situation in this country.

Excellent commercial electroencephalographic apparatus, that more than meets the EEG Societies' specifications, is readily available in South Africa. There is a choice of instruments and the prices are not excessive.

EEG recordists, those persons who take the records and who are responsible for manipulating the instrument's controls in such manner as may make or mar a record as a diagnostic test, have no systematic training for their work in this country. Overseas such training is a commonplace to-day, for a recordist who is capable of an accurate general appraisal of a record as it is running, and who usually knows when to seek the opinion of the trained clinical electroencephalographer, is in a most responsible position in any EEG Department. She must know something of the significance of EEG records and should deal with patients with the respect to which all are entitled; electronics is not part of the training just as automotive engineering knowledge is not required to obtain a driver's licence.

The EEG Societies consider that the optimum experience for the clinical electroencephalographer should include practical experience in experimental neurophysiology and in clinical neurology besides 1 to 2 years' *full-time* training in EEG interpretation under competent guidance. Failing the aforementioned qualifications, then either a University-trained neurophysiologist or a neurologist without physiological *experience* could become responsible for an EEG Department provided they had the required period of full-time training in EEG diagnosis. However, the EEG Societies' Committee states:

> 'It should be understood by everyone concerned that a medical man who is ignorant of physical principles and physiological methods is as much a menace to high standards of service as is a non-medical man who is unacquainted with the clinical import of his observations.'

The requirements of training are not easy, but then it is not easy to set a standard of interpretation which raises electroencephalography to a place among the most important

diagnostic techniques within clinical neurology. I am of the opinion that few South Africans will believe that EEG diagnosis is, in its sphere,[3] almost if not quite as valuable as special X-ray methods in neurology. However, to proclaim that EEG diagnosis 'just is' unreliable, without knowing most of the requirements of the International Federation of EEG Societies is to expose self-confessed ignorance.

The tragedy is this: not only may patients who have EEG tests fail to benefit as fully as they should from the examination, but countless other patients who should have an EEG, to benefit from an early diagnosis, do not have the investigation done.

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NOTES AND NEWS : BERIGTE

Mr. Len Stein, F.R.C.S. (Edin.), has moved his consulting rooms from Lister Buildings to 202 Osler Chambers, corner Jeppe and Delvers Streets, Johannesburg.

His telephone numbers (which are not in the current directory) remain the same, *viz.*: *Consulting Rooms*: 23-7803; *Residence*: 41-2231; *Emergency*: 22-4191.

* * *

MERCK SHARP AND DOHME INTERNATIONAL

Merck Sharp & Dohme International, Division of Merck & Co., Inc., U.S.A., announce the activation of its South African company, Merck Sharp & Dohme (S.A.) (Pty.) Limited, to conduct the interests and promotional activities of the company in South Africa.

In addition plans are in progress to broaden the scope of the South African company to cover limited local manufacture of selected products. It is anticipated that this will be the first stage in a gradually expanding local manufacturing programme. The company has manufacturing facilities in many parts of the world, including Great Britain, Canada, Holland, Australia, Japan, Philippine Islands, Mexico, Argentine and Brazil.

Development of these plans in South Africa is in recognition of the needs of the market in a rapidly growing economy.

It is expected that the promotional company will occupy new offices about June next in a multi-storey building now being built on Smal Street between Pritchard and President Streets, Johannesburg.

Merck Sharp & Dohme Products will continue to be distributed to the wholesale trade through the firm's presently established distributors: S.A. Druggists Limited Agency Division (Sharp & Dohme Line) and Mulphico Pharmaceuticals (Pty.) Ltd. (Merck Line).

Further announcements will be made at a later date.

* * *

CROSS INFECTIONS IN HOSPITALS

A 30-minute motion picture dealing with the overall world-wide problem of cross infections in hospitals will be produced co-operatively by the American Medical Association, the American College of Surgeons and the American Hospital Association. This timely and basically import film has been made possible by the co-operation and support of Johnson & Johnson of New Brunswick, New Jersey.

The film, which will be in sound and colour, is designed to educate all levels of hospital personnel concerning the many avenues by which infection can be spread throughout a hospital and will utilize the staphylococcus by way of illustration and as an example of one of the most important phases of the problem.

Produced under the supervision of Dr. Carl Walter of Boston, Associate Clinical Professor of Surgery, Harvard Medical School, one of the recognized pioneer investigators in this field, and a committee representing the AMA, ACS and AHA, it will deal with the broad fundamentals of phases of the problem and lay the groundwork for the delineation of the problems relating to specific fields in a series of shorter films to follow.

The presentation will have its premiere showing at the annual meeting of the American Medical Association in Atlantic City in June 1959, again at the conclave of the ACS in October, and subsequently at professional gatherings throughout the world.

The production of this film will be co-ordinated by Ralph P. Creer, Chicago, Director of Motion Pictures and Medical Television of the American Medical Association.

* * *

SMITH, KLINE AND FRENCH LABORATORIES GRANT FOR THE STUDY OF SOUTH AFRICAN PLANTS

The Council for Scientific and Industrial Research have received a grant of £3,500 (S.A.) for a study of South African plants to determine whether they contain chemical agents which might be valuable as new drugs. The grant was made by Smith Kline & French Laboratories, Philadelphia, U.S.A., parent firm of SKF Laboratories (Pty) Ltd., Port Elizabeth.

Although several studies have been made of the rich South Africa flora, these have largely concerned the toxic effects of native plants on animals. The CSIR study, however, will be oriented towards identification of chemical substances which might have useful therapeutic properties in humans. Special attention will be directed to substances traditionally used in local folk medicine.

In research of this sort, plants are first identified botanically. Then chemists isolate the plant constituents, which in turn are tested by the pharma-

cologist for medicinal properties. Promising drugs are tried in the clinic.

Although more and more pharmaceutical agents are made synthetically, scientists are again turning their attention towards plants as sources of leads for new drugs. For example, one class of tranquilizing agent has developed from studies of a snake-like root which has been used in India for centuries.

Another factor in this search is that once chemists have extracted and identified a medically active substance, it is frequently possible to reproduce the molecule of the chemical and, in the process of synthesis, to alter the molecular structure so that undesirable side effects are eliminated in whole or in part.

The parent firm of SKF Laboratories (Pty) Limited is engaging in similar studies of plant life in other regions of the world.

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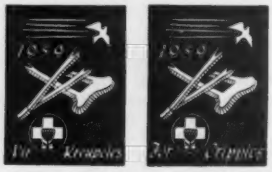
THE EASTER STAMP FUND

The annual Easter Stamp Fund campaign is the National Council for the Care of Cripples' only call on the people of South Africa.



The first sale of stamps in 1944 brought in but a few thousand pounds. In the succeeding years, increased need was met with increasing generosity and the total has moved up steadily each and every year.

There is no limit to the work Easter Stamps can achieve. The Council is prepared to do the work. All it asks is that at Easter Time generous support will be continued.

• • •

DIE PROFESSIONELE VOORSIENINGSVERENIGING VAN SUID-AFRIKA

TWEE VERDERE DRINGENDE BEHOEFTES VAN PROFESSIONELE PERSONE NOU BEVREDIG

Die ongekende welslae van die Vereniging wat voortdurend nuwe hoogtes bereik het die Raad aangemoedig om sy dienste uit te brei. Twee verdere uitstaande opsionele voordele is bygevoeg tot die ongeëwenaarde onbevoegdheid en voorsienings fonds —voordele wat reeds beskikbaar is vir lede van die volgende professionele organisasies:

Die Tandheelkundige Vereniging van Suid-Afrika.

Die Geneeskundige Vereniging van Suid-Afrika.

Die Aptekersvereniging van Suid-Afrika.

Die Algemene Raad van die Balie van Suid-Afrika.

Die Vereniging van Wetsgenootskappe van Suid-Afrika.

Die Suid-Afrikaanse Veterinêr-Mediese Vereniging.

Die Sentrale Landmetersraad van die Unie van Suid-Afrika.

Handelende op die magtiging gegee by die 1958 jaarlikse algemene vergadering het die Raad onderhandelings vir 'n Groeplewensskema asook 'n Hospitalisasieskema suksesvol afgehandel. Die volgende is baie kort opsommings van hierdie skemas wat albei in werking tree op 1 November 1958 en wat opgestel is vir alle lede van die Vereniging.

1. *Groeplewensversekeringskema*: By enige man met 'n verantwoordelikheidssin spook die vrees dat hy sy afhanklikes in finansiële moeilikheid mag agterlaat en die mees dringende onmiddellike behoefte is om voldoende voorsiening vir hulle te maak vir die geval van sy dood, teen 'n redelike jaarlikse koste. Die goedkoopste vorm van dekking word verskaf deur groepversekering en die Vereniging onder leiding van sy Aktuaris het nou 'n tender aangeneem vir die onderskrywing van so 'n skema, soos voorgelê deur die Suid-Afrikaanse Nasionale Lewensassuransie-Maatskappy Beperk (SANLAM). Die skema wat ontwerp is, beliggaam besonder aantreklik voordele teen uiters lae premietariewe. Dit stel bestaande lede wat aansluit binne drie maande vanaf aanvang van die skema in staat om aan te sluit sonder om bewys van versekerbaarheid te moet lewer—'n uiters waardevolle toegewing aan diegene wat alreeds hul jare gekry het. Hierdie toegewing word tot 12 maande uitgebrei in die geval van diegene wat by die Vereniging aansluit na aanvang van die skema. Lidmaatskap van die skema mag voortgesit word na die aftree-ouderdom van die Vereniging bereik is, onderhewig aan sekere reëls van die skema. Die versekerede bedrag word in elke geval bepaal in verhouding tot die aantal aandele of lidmaatskapeenhede; die lid het die keuse om dekking te neem van £20 of veelvoude daarvan tot 'n maksimum van £100, vir elke aandeel wat hy hou. Die maksimum versekerde bedrag vir 'n lid wat die maksimum aantal aandele van 50 hou is dus £5,000. Die huidige premietarief van 1s. 3d. persent per maand is gelyk aan £7 10s. per £1,000 per jaar of 'n skrale £37 10s. per jaar vir £5,000. Die skmea maak voorsiening vir toekenning van winste aan die Vereniging en die Raad het die mag om sulke winste te belê. Vir sekere doeleindes soos studielenings en vennootskappe mag voordele onder die skema sedeer word aan die Vereniging wat die verstrekking van waarborge ten behoewe van die lid sal oorweeg.

2. *Hospitalisasieskema*: Hierdie skema is ontwerp ten einde lede te help om die aansienlike koste betrokke by hospitalisasie vir hulself en hulle afhanklikes te kan bestry. Dekking is onmiddellik en geen bewys van versekerbaarheid sal vereis word vir bestaande lede wat binne ses maande vanaf aanvang van die skema aansluit en nuwe lede van die Vereniging wat binne drie maande vanaf aansluiting van die Vereniging by die skema aansluit. Die Vereniging sal aan die lid 'n toelae betaal van £2 per dag van verblyf in Hospitaal of verpleeginrigting of siekte tuis, onder mediese toesig, met 'n geregistreerde verpleegster teenwoordig onderhewig aan 'n maksimum van 200 voordeeldae vir die getroude man en sy gesin en 100 voordeeldae vir 'n ongetroude lid gedurende enige lidmaatskapjaar. 'n Spesiale poliovoordeel insluitende sekere mediese onkoste tot 'n maksimum van £1,000 in enige lidmaatskapjaar wat ontstaan na ten minste een jaar se lidmaatskap, word, verskaf. Die bogemelde toelae sal toegelaat word ten opsigte van bevallings indien dit voorkom ten minste ses maande na aanvang van

lidmaatskap. Die bydraetariewe is 4s. per maand vir 'n ongetroude lid en 10s. per maand vir 'n getroude lid ongeag van die aantal afhanklikes.

Voorsiening is gemaak vir lidmaatskap om voortgesit te word teen effens verhoogde tariewe nadat die Vereniging se aftree-ouderdom bereik is en by die dood van 'n manlike lid sal sy afhanklikes lidmaatskap mag voortsit teen verminderde koste. Hierdie skema mag mettertyd uitgebrei word om 'n volle mediese assuransieskema te omvat.

Albei hierdie opsionele addisionele voordele is besonder waardevol vir lede, hetsy hulle nog jonk is of reeds die aftree-ouderdom nader en bestaande lede behoort onmiddellik te sorg dat hulle deelname verseker word. Diegene wat nog nie lede van die Vereniging is nie, behoort nie langer uit te stel om vir hulself die voordeel te verkry van die omvattende sekuriteit wat verskaf word deur lidmaatskap van die Vereniging nie. Navrae moet deurgaans gerig word aan die Sekretaris, Posbus 6268, Johannesburg.

PREPARATIONS AND APPLIANCES

ENDOSCOPIC SURGERY OF THORACIC AUTONOMIC NERVOUS SYSTEM

Medical Distributors (Pty) Ltd. have been appointed Sole Distributors for Endoscopic Neurosurgical Equipment as used by Kux in Innsbruck.

Considerable advances have been made in the last decade in the surgery of the autonomic nervous system in the thorax, using an endoscopic approach. Kux started using this method extensively to examine and resect abnormal parts of the chain in 1947. In 1954, after having performed over 1,000 of these cases, he published *Thorakoskopische Eingriffe am Nerven System* (Georg Thieme, Stuttgart). Since this time other workers (including Roedling, Roth and McCarthy) have been using this technique.

Fig. I. Needle.

Fig. II. Cautery loop.

Fig. III. Thorascope assembled.

The procedure is usually carried out under local anaesthesia, using a special neurosurgical instrument. This instrument includes trocar and needle for injection of the anaesthetic, cautery tips and different optical systems, all of which can be changed through the cannula.

For further details of these instruments please write to:

Medical Distributors (Pty) Ltd., P.O. Box 3378, Johannesburg, or P.O. Box 3077, Cape Town.

GEWODIN

ANALGESIC AND ANTIPYRETIC

This is a completely new formula of an analgesic/antipyretic preparation which is a real innovation in the field of such remedies. The formula for *Gewodin* is:

3-(N-methyl-(a-methyl-B-phenil)-ethyl-aminomethyl)-4-isopropylnorantipyrin	0.025 g.
Dimethylaminoantipyrin	0.100 g.
p-Acetophenetidin	0.200 g.
Caffeine	0.030 g.

Indications: Symptoms due to weather changes; headaches—migraine; rheumatic pains—neuralgia; dysmenorrhoea; toothache; colds and chills—influenza.

Tolerance: There are no side-effects referred to the gastro-intestinal tract or to the circulatory system, nor are there any allergic manifestations even in patients who have taken several tablets a day (3 to 5) for several weeks.

Dosage: *Adults*: 1–2 tablets up to 3 times daily. *Children*: ½–1 tablet daily.

Presentation: Boxes of 10 tablets; Boxes of 100 tablets; Hospital packings.

Further details may be obtained from the sole South African distributors: Petersen Ltd., P.O. Box 5785, Johannesburg; P.O. Box 38, Cape Town; P.O. Box 1684, Durban.

SIQUIL (TRIFLUPROMAZINE)

A POTENT PSYCHIC STABILIZER

Squibb Laboratories (Pty.) Limited announce the introduction of *Siquil*—Squibb triflupromazine, a new and better agent for the management of the mentally disturbed.

Description: *Siquil* is a psychic stabilizer for the treatment of the highly agitated. Although a phenothiazine derivative, it is more potent, faster acting and much safer than the older phenothiazines.

Action: *Siquil* appears to exert its full effect on the emotions and leave the intellect clear. In contrast to other phenothiazines, it places patients in the stable zone, free from jitters and lethargy. Because of its stabilizing effect on behaviour, *Siquil* is particularly useful in the management of psychomotor hyperactivity and overt hostility.

The Candidates for Siquil: Highly agitated, excited patients; senile, agitated psychotics; ambulatory schizophrenics; elderly persons with organic brain disease; patients in the manic phase of affective psychoses; assaultative combative patients; highly agitated menopausal women; patients with post-alcoholic tremors and delirium.

Easier to Handle: *Siquil* is much less prone to give rise to side effects than chlorpromazine, promazine, prochlorperazine, mepazine and perphenazine. No jaundice or convulsions have been observed. Hyperthermia and skin eruptions are rare. Parkinson-like symptoms which have been associated with other phenothiazine therapies occur much less frequently with *Siquil* and are readily reversible with reduction or discontinuance of medication for two or three days.

Control of Nausea and Vomiting: *Siquil* possesses more potent antiemetic properties than chlorpromazine. Often it confers prompt relief after failure of standard antiemetics and other phenothiazine drugs.

More Potent: With recommended average dosage, *Siquil* has twice the potency, on a weight-for-weight basis, of chlorpromazine. As dosage increases (as may be necessary in severe cases) it surpasses the potency of chlorpromazine even more—with *Siquil* outstripping chlorpromazine three to five times.

Dosage: For psychic stabilization: Usually initial dosage is 25 mg. *t.i.d.* to be adjusted according to patient response. Caution should be exercised in administering daily doses in excess of 300 mg.

Precautions: Although *Siquil* has produce remarkably few side effects, it is recommended that the same precautions that apply to other phenothiazine derivatives be observed.

Contraindications: *Siquil* is contraindicated in comatose states, due to central nervous system depressants (alcohol, barbiturates, opiates).

PREPARATE EN TOESTELLE

ENDOSKOPIESE CHIRURGIE VAN DIE TORAKALE OUTONOMIESE SENUWEESTELSEL

Medical Distributors (Edms.) Bpk. is aangestel as die Uniale Versspreiders van Endoskopiese Neurochirurgiese Apparaat soos gebruik deur Kux in Innsbruck.

In die afgelope dekade is daar heelwat vooruitgang gemaak in die chirurgie van die outonomiese sisteem in die torakale holte, deur gebruik van 'n endoskopiese benadering. In 1947 het Kux ekstensief begin om deur middel van hierdie metode te ondersoek en reseksteer. In 1954, nadat dr. Kux reeds meer as 1,000 gevalle behandel het, het hy 'n boek, *Thorakoskopische Eingriffe am Nerven System*, oor hierdie onderwerp opgestel (Georg Thieme, Stuttgart). Sedertdien het ander werkers (insluitende Roedling, Roth en McCarthy) van hierdie tegniek gebruik gemaak.

Fig. I. Naald.

Fig. II. Skroeipunte.

Fig. III. Saamgestelde Torakoskoop.

Hierdie operasie word gewoonlik onder lokale verdowing uitgevoer deur gebruik te maak van spesiale neurochirurgiese instrumente. Die apparaat sluit onder andere in 'n trokar en naald, om die verdowingsmiddel toe te dien, skroeipunte en verskeie optiese sisteme. Al hierdie toebehore word deur 'n spesiale cannula gebruik.

Vir nadere besonderhede omtrent die instrumente, skryf asseblief aan:

Medical Distributors (Edms.) Bpk., Posbus 3378, Johannesburg of Posbus 3077, Kaapstad.

GEWODIN

'N PYNSTILLENDE EN KOORSWERENDE MIDDEL

Dit is 'n volkome nuwe formule vir 'n pynstillende en koorswerende preparaat, en is 'n egte nuwigheid op die gebied van hierdie soort middels. Die formule van *Gewodin* is:

3-(N-metiel-(a-metiel-B-feniel)-etiel-amino-metiel)-4-isopropielnorantipirien	0.025 g.
Dimetielamino-antipirien	0.100 g.
p-Asetofenetidien	0.200 g.
Kaffeïen	0.030 g.

Indikasies: Simptome wat aan weersveranderings te wyte is; hoofpyn—migraine; rumatiekpyn—sinkings; dismenoree; tandpyn; verkoues en influensa.

Verdraamsaamheid: Daar is geen newe-effekte vir sover dit die maagdermkanaal of die bloedsomloopstelsel betref nie. Ook is daar geen allergiese manifestasies nie, selfs nie eens by pasiënte wat etlike weke lank 'n hele paar tablette (3 tot 5) per dag geneem het nie.

Dosis: *Volwassenes*: 1–2 tablette tot 3 maal per dag. *Kinders*: ½–1 tablet per dag.

Aanbieding: Dosies van 10 tablette; dosies van 100 tablette; hospitaalverpakkings.

Nadere besonderhede kan verkry word van die Alleenverspreiders vir Suid-Afrika:

Petersen Ltd., Posbus 5785, Johannesburg; Posbus 38, Kaapstad; Posbus 1684, Durban.

SIQUIL (TRIFLUPROMASIEN)

'N KRAGTIGE PSIGIESE STABILISEERMIDDEL

Squibb Laboratories (Pty.) Limited kondig die beskikbaarstelling aan van *Siquil*, Squibb se triflupromasien, 'n nuwe en beter middel vir die behandeling van geestelik versteurdes.

Beskrywing: *Siquil* is 'n psigiese stabiliseermiddel vir die behandeling van pasiënte wat hoogs opgewonde is. Hoewel dit 'n fenotiasienderivaat is, is dit kragtiger en veiliger, en werk dit vinniger as die ouer fenotiasiene.

Effek: Dit skyn asof *Siquil* sy volle effek op die emosies uitoefen, en die intellek heeltemal helder laat. In teenstelling met die ander fenotiasiene plaas dit die pasiënt in die stabiele streek, sonder enige opgewondenheid en lusteloosheid. Met die oog op die stabiliserende effek wat dit op gedrag het, is *Siquil* veral nuttig vir die bestryding van psigomotoriese hiperbedrywigheid en selfs vyandigheid.

Wie met Siquil Behandel Kan Word: Hoogs verontruste, opgewonde pasiënte; bejaarde, verontruste psigotiese pasiënte; ambulatoriese skisofreniese pasiënte; bejaarde persone wat aan organiese breinsiektes ly; pasiënte in die maniese fase van gemoedspsigoses; aanvallende, strydlustige pasiënte; hoogs opgewonde vroue in die menopause-periode; pasiënte wat ly aan na-alkoholiese bewing en ylhoofdigheid.

Makliker Behandeling: *Siquil* sal waarskynlik aanleiding gee tot minder newe-effekte as chloorpromasien, promasien, prochloorperasien, mepasien en perfenasien. Geen geelsug of stuiptrekkings is waar-

geneem nie. Koorsagtigheid en huiduitslag is seldsame verskynsels. Die Parkinson-agtige simptome wat met ander fenotiasienbehandeling geassosieer word, kom minder dikwels voor as *Siquil* voorgeskryf word, en kan maklik teëgewerk word deur die dosis te verminder of die behandeling 'n dag of twee lank te staak.

Beheer oor Mislikheid en Braking: *Siquil* besit kragtiger brakingsbestrydingseienskappe as chloorpromasien. Dikwels besorg dit vinnige verligting aan die pasiënt nadat standaard-brakingsbestrydings- en ander fenotiasienmiddels misluk het.

Kragtiger: Teen die aanbevole gemiddelde dosis is *Siquil* twee keer sterker, op 'n gewig-vir-gewig-grondslag, as chloorpromasien. As die dosis vermeerder word (en dit kan wenslik wees in ernstige gevalle) oortref dit die sterkte van chloorpromasien nog verder. Teen die hoër dosis is *Siquil* drie tot vyf keer sterker as chloorpromasien.

Dosis: Vir psigiese stabilisasie: die gewone aanvanklike dosis is 25 mg. *t.i.d.* Dit word dan aangepas na gelang van die pasiënt se reaksie. Versigtigheid moet aan die dag gelê word by die toediening van daaglikse dosisse van meer as 300 mg.

Voorsorgsmatreëls: Hoewel *Siquil* merkwaardig min newe-effekte het, word daar aanbeveel dat dieselfde voorsorgsmaatreëls wat in die geval van die ander fenotiasienderivate toegepas word, in ag geneem moet word.

Kontra-indikasies: Daar is kontra-indikasies vir die gebruik van *Siquil* in die geval van bewustelose pasiënte, waar die bewusteloosheid deur sedatiewe van die sentrale senuweestelsel veroorsaak is (alkohol, barbiturate, slaapmiddels).

REVIEWS OF BOOKS

ANKLE FRACTURES

Operative Treatment of Ankle Fractures. By Sverre Vasli. 1957. (Pp. 74. With Figs. 19s. 6d.). Oslo: Oslo University Press. *Sole South African Distributor*: P. B. Mayer, P.O. Box 713, Cape Town.

This most interesting and informative publication sets out very clearly, and in a most readable manner, present-day trends in the treatment of ankle fractures in Oslo. It gives a comprehensive review of the investigations carried out over an 8-year period of all cases of ankle fractures dealt with conservatively and by open reduction in Alleval Hospital.

Experiments carried out on cadavers or amputated material reproduced the ankle injuries, and X-ray examination of these injuries has made possible a classification according to the injury mechanism, and not on purely anatomical lines.

The classification put forward by Hansen in 1942 is adopted by the author, and there are excellent pen drawings to illustrate the classification.

A chapter is devoted to the method of treatment, followed by the operative procedure which has been developed at Alleval Hospital. A careful follow-up study of the cases treated has shown that the method of treatment, based on principles of open reduction with internal fixation and early mobilization, best fulfil the requirements of successful management of ankle joint fractures.

The text is well written and well illustrated. The material is highly specialized and should interest the individual orthopaedic surgeon, with jumping-off places for further research in the treatment of ankle fractures.

FOG, SMOG AND ENVIRONMENTAL SANITATION

Expert Committee on Environmental Sanitation, Fifth Report: Air Pollution. World Health Organization: Technical Report Series, 1958, No. 157. (26 pages. 1s. 9d.). Pretoria: van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724.

The serious effect of contaminated air on health has been dramatically demonstrated in recent years in several fogs or smogs, such as those in the Meuse Valley in Belgium (1930), in Donora in the USA (1948) and on several occasions in London. Together, these incidents caused the deaths of thousands of people. Less virulent air pollution of long standing, however, may be equally serious in its more wide-spread and insidious threat to human well-being, and in its economic effects. At the end of 1957 the World Health Organization's Expert Committee on Environmental Sanitation decided to consider the health hazards of man-made air pollution, and to suggest preventive and remedial action which might be taken in individual countries.

The participants in this Committee represented 4 continents and the fields of public health administration, sanitation, physics, industrial hygiene, fuel research and meteorological research. In their *Report* they discuss first the problem of the recognition and evaluation of potential or actual conditions of air pollution with particular reference to the gaseous, liquid and solid contaminants produced by industrial and domestic sources, from fuels, and from radiochemical and nuclear processes. It is pointed out that the many factors which have to be taken into account (wind flow, turbulence, temperature inversions, precipitation and topographical influences) call for the standardization of sampling techniques, instruments and reporting terminology, and also for further methodological research.

Considering next the effects of pollution on man, animals, plants and the economy, the Committee concludes that far too little is as yet known for desirable limits of concentration of contaminants to be established. It is suggested that laboratory investigation of suspect substances should be greatly expanded; and that specific epidemiological research should be carried out on those diseases (such as chronic bronchitis and lung cancer) thought to be causally related to air pollution, international agreement being sought on the relevant clinical and statistical terms. Animal and botanical studies may be particularly valuable not only for their intrinsic economic importance but even more for the guidance to be thus obtained on parallel human susceptibility. Certain plants, moreover, might be of use as alarm signals of potential danger to human health.

Turning to the questions of prevention and control of air pollution, the Committee emphasizes that much of the pollution which now exists could be prevented without undue cost, and sometimes even with a financial saving, by careful planning and siting of factories and dwellings, better design of equipment, and better operation of equipment based

on adequate training of management, executives and operators. The administration of a control programme must be based upon the concept that clean air is attainable to the extent that the community concerned is willing to pay for it; public education on the question should be inaugurated to facilitate the activities of the control authority. New legislation will be necessary to provide for a workable control organization. It is proposed that advice on this aspect might be obtained from national committees representing the interests of public health administration, fuel usage, industrial hygiene, agriculture, science, industry and town planning. The Committee considers that, while the control programme should be placed primarily in the hands of existing public health departments, it should be administered by officials who have received specialized technical training, and that national advisory councils on air pollution should be appointed to appraise the problem as a whole and to maintain a supervisory watch on the various features of each country's effort.

NON-VENEREAL SYPHILIS

Non-Venereal Syphilis: A Sociological and Medical Study of Bejel. By Ellis Herndon Hudson, M.D., D.T.M. & H. (Lond.), F.A.C.P. (Pp. 204 + viii; illustrated, 30s.). Edinburgh and London: E. & S. Livingstone Ltd. 1958.

The announcement of a new work by the House of Livingstone is always an indication that something of enduring value is about to appear in the world of medical literature. The present work by Dr. Hudson is no exception to this rule. In gathering material for his book Dr. Hudson could not have chosen a better place than the small Arab town of Deir-ez-Zor on the Euphrates, which is 210 miles down the river from the railhead at Aleppo, and 300 miles across the desert from Damascus. Over a period of 12 years, Dr. Hudson treated over 10,000 cases of bejel, and throughout this time he carefully recorded his observations with respect to the clinical, serological, epidemiological and therapeutic aspects of the bejel problem.

Bejel, the author reminds us, is the name given to a form of non-venereal syphilis which is endemic in the backward rural areas of Yugoslavia, Turkey, Syria, Iraq, Arabia, North Africa and in the Americas. The special importance of bejel lies in the fact that the child is a reservoir of the disease. The primary sore, if present, is seldom recognized, while the early stage consists of a muco-cutaneous eruption closely resembling the secondary stage of venereal syphilis. The mouth lesions of the affected child are very highly infective, so that the transmission of infection from one child to another, from one family to another, and from one community to another becomes a very simple matter—especially in an unhygienic environment engendered by poverty, slums and overcrowding.

In the absence of specific therapy, most cases of endemic syphilis eventually progress to the late stage, which consists of lesions in the bones and skin, and often in the mouth, nose and throat. A striking feature of this form of syphilis lies in the fact that the cardio-vascular system and the central nervous system are seldom, if ever, involved.

The social havoc wrought by the disease is considerable, and when we learn that 90% of the peasantry, living in the backward rural areas referred to, contract the disease in childhood, then we feel that we can with much justification laud the pioneer work of Dr. Hudson as an officer of the World Health Organization. His latest work on the bejel problem, which represents an expansion of his earlier 26 articles on the subject, will remain a fine memorial to his humanitarian endeavours in 'less happier lands.'

CORRESPONDENCE

ELECTROENCEPHALOGRAPHY AT THE JOHANNESBURG HOSPITAL

To the Editor: I have read the MS. of the article (which appears elsewhere in this issue) by Dr. M. Wright, who is not unique in attacking conditions in South Africa. The Electroencephalographic Laboratory is not a department of the General Hospital, Johannesburg, although all hospital cases are referred to this laboratory. We comply with the requirements which Dr. Wright has enumerated in his criticism. It is to be noted that during Dr. Wright's appointment to this department, he never raised any of the objections he has brought forward in his article.

S. Jacobson,
M.Sc., M.B., B.Ch., M.R.C.P.E., D.P.M.

Electroencephalographic Laboratory,
Princess Nursing Home,
Johannesburg.

A COURSE IN ELECTROCARDIOGRAPHY

To the Editor: There have been numerous requests for a repetition of the courses organized by the S.A. Society of Occupational Health last year, as they proved of immense value to members of the profession.

The Society has pleasure in announcing a lecture course, which is supported by the Witwatersrand University Graduate Association, on:

An Introductory Course to Electrocardiography.

The course of lectures will be delivered by Dr. Leo Schamroth, of Baragwanath Hospital.

The lectures will begin on Tuesday, 3 March, 1959, at 5.30 p.m. in the lecture theatre of the South African Institute for Medical Research, Hospital Hill, Johannesburg, and will continue at the same time and place every Tuesday thereafter.

N.B.—Attendance at the first lecture is imperative as it forms the basis for all subsequent lectures.

The fee for the course is £3 3s.

Please notify the Honorary Joint Secretaries by letter of your intention to attend the course and remit your cheques to: The S.A. Society of Occupational Health, c/o Dr. B. Serebro, *for the* Honorary Joint Secretaries, 129 Union Centre, 31 Pritchard Street, Johannesburg.

B. Serebro,
Honorary Secretary.

129 Union Centre,
31 Pritchard Street,
Johannesburg.

Published by the Proprietors Juta and Co. Ltd., 43 Pritchard Street, Johannesburg, and printed in the Union of South Africa by Cape Times Limited, Parow, C.P.

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